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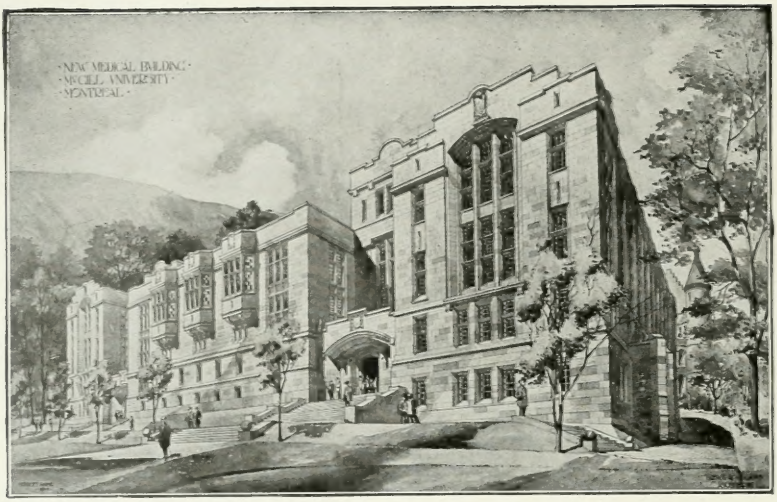

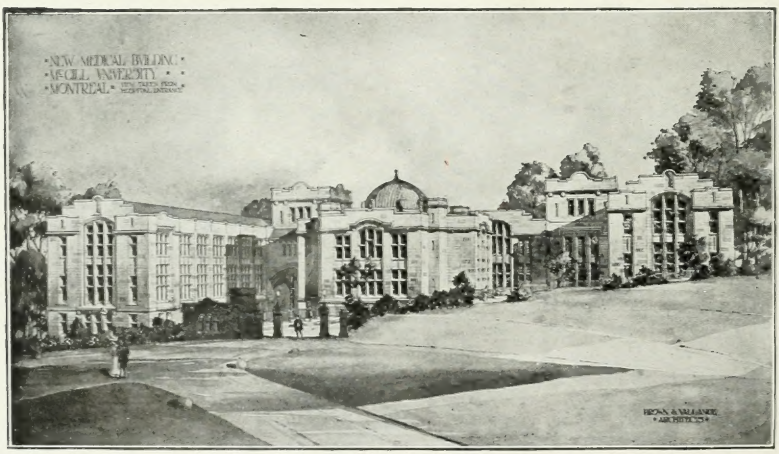

New Medical Building of McGill University, where the Therapeutic Society meeting of 1912 was held.

TRANSACTIONS

OF THE

American Therapeutic Society

1912

EDITOR

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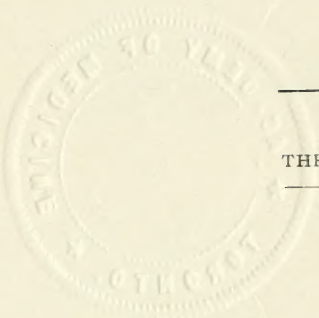

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THE AMERICAN THERAPEUTIC SOCIETY

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Kolipinski, L.	631 I St., N. W.	Washington, D. C.

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Van der Veer, Albert	38 Eagle St.	Albany, N. Y.
Van Rensselaer, Howard	123 State St.	Albany, N. Y.
Wheatley, Frank George	174 North Adams St.	North Abington, Mass.
White, John Blake	1013 Madison Ave.	New York, N. Y.
Wilcox, Reynold Webb	679 Madison Ave.	New York, N. Y.
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Wood, H. C., Jr.	434 S. 44th St.	Philadelphia, Pa.

HONORARY MEMBERS.

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Hayem, Georges	Paris, France
Marshall, C. R.	Dundee, Scotland
Schoeler, Heinrich	Berlin, Germany
Tillmanns, Hermann	Leipsic, Germany

EX-PRESIDENTS.

Horatio C. Wood	Philadelphia, Pa.	1900-1
Reynold Webb Wilcox	New York, N. Y.	1901-2
Thomas E. Satterthwaite	New York, N. Y.	1902-3
* Howard H. Barker	Washington, D. C.	1903-4
Oliver T. Osborne	New Haven, Conn.	1904-5
* Carl Beck	New York, N. Y.	1905-6
* Robert Reyburn	Washington, D. C.	1906-7
* John V. Shoemaker	Philadelphia, Pa.	1907-8
Frederic H. Gerrish	Portland, Me.	1908-9
James C. Wilson	Philadelphia, Pa.	1909-10
Harvey W. Wiley	Washington, D. C.	1910-11
Alexander D. Blackader	Montreal, Can.	1911-12

* Deceased.

DECEASED MEMBERS

Samuel Claggett Busey, M.D., LL.D., died Oct. 19, 1899.
William P. Manning, M.D., died Feb. 9, 1901.
John Thomas Winter, M.D., LL.D., died June 22, 1902.
George Edward Tyler, M.D., died July 7, 1902.
Robert Henderson Graham, M.D., died Aug. 24, 1903.
George Bingham Fowler, M.D., died March 6, 1907.
John S. McLain, M.D., died June 2, 1907.
Robert Reyburn, M.D., died March 25, 1909.
Justin Steer, M.D., died June 20, 1909.
Howard H. Barker, M.D., died May 8, 1910.
John Veitch Shoemaker, M.D., died October 11, 1910.
Carl Beck, M.D., died June 8, 1911.
Henry Alfred Robbins, M.D., died October 26, 1911.
John Herr Musser, M.D., died April 3, 1912.
Louis Nelson, A.M., M.D., died April 14, 1912.

CONSTITUTION AND BY-LAWS.

ARTICLE I.

This Society shall be known as the American Therapeutic Society.

ARTICLE II.

The object of this Society shall be the promotion of therapeutics in its broadest sense.

ARTICLE III.

This Society shall meet annually at such time and place as the Council may determine.

ARTICLE IV.

SECTION 1. The Officers of this Society shall consist of a President, three Vice-Presidents, a Secretary, a Treasurer, and a Council of fifteen members, all to be elected from the active membership, by ballot, at an annual meeting.

SECTION 2. The Council may be convened at any time by the Chairman, at the request of any three of its members. Its decisions shall be equivalent to acts o fthe Society, and shall be reported to it at the next regular meeting. The Council shall elect from its members a Committee on Admissions to consist of three members.

SECTION 3. A vacancy occurring in any office may be filled by the Council.

ARTICLE V.

SECTION 1. This Society shall consist of not more than one hundred active members. Honorary members may be elected on recommendation of the Council.

SECTION 2. Any qualified physician engaged in the general or special practice of medicine or surgery, or in laboratory research of interest in the treatment of disease, is eligible for membership.

SECTION 3. Applications for membership should be made in writing at least one month before the annual meeting. They are to be referred to the Committee on Admissions, which shall, on approval, present their names to the Society at the annual meeting. Five negative ballots shall reject an applicant.

SECTION 4. Applications for membership shall be accompanied by the annual dues for the ensuing year.

SECTION 5. Resignation of members shall not be accepted until all dues have been paid.

ARTICLE VI.

All proposed changes of the Constitution must be offered in writing at a regular meeting. They are to be considered only at an annual meeting, when a two-thirds vote of the members present shall be necessary for their adoption.

BY-LAWS.

1.

The *President* shall preside at the annual meeting of the Society, and deliver an address. He shall appoint a Committee on Scientific Business and a Committee of Arrangements.

In the absence of the President, one of the Vice-Presidents shall preside.

2.

The *Secretary* shall keep a record of the transactions of the Society and of its Committees, conduct all correspondence of the Society, and mail to each member a programme of the meeting, at least two weeks before it is held. The records, publications and seal of the Society shall be in his custody.

The *Treasurer* shall collect all moneys due the Society, disburse the same, as directed by the Council, keep a proper account of all his transactions, and render an annual statement to the Society. He shall have charge of all property belonging to the Society not otherwise provided for.

3.

Ten active members shall constitute a quorum for the transaction of business.

4.

SECTION 1. The *Council* shall constitute a standing committee to consider all matters of interest to the Society. It shall elect a Chairman, Vice-Chairman and a Secretary, and shall appoint an Editor of the Transactions.

SECTION 2. Three members of the *Council* shall be elected annually by the Society, each to serve five years.

SECTION 3. Five members shall constitute a quorum.

5.

The *Committee on Admissions* shall investigate the qualifications of applicants and report at the next annual meeting.

6.

Charges against any member must be made in writing. They shall be referred to the *Council* for investigation.

7.

No papers, report, abstract or other communication, either written or verbal, which, directly or indirectly, commends or advocates any secret, patented or trade-marked product or method of treatment shall be presented to or received by the Society; nor shall any discussion on such product or method be permitted.

Papers are limited to twenty minutes and discussions to five minutes.

8.

The *annual dues* shall be five dollars, payable in advance.

9.

The *order of business meetings* shall be as follows:

1. Reading of Minutes.
2. Reports of Officers and Committees.
3. Election of Members.
4. Presentation of Communications.
5. Miscellaneous Business.
6. Election of Officers.

COMPETITIVE THERAPEUTIC RESEARCH.

On recommendation of the Council of the American Therapeutic Society, at the annual meeting of the Society held in Montreal, Canada, June 1, 1912, it was voted that prizes of two hundred and fifty dollars ($250.00), one hundred and fifty dollars ($150.00) and one hundred dollars ($100.00) be awarded to the best reports on subjects relating to Therapeutics, on the following conditions:

1.—The competition is to be limited to qualified physicians in the United States and Canada.

2.—The subject of the competition is to be limited to a substance or preparation which is official in the United States Pharmacopœia.

3.—The research may be either wholly laboratory or clinical, or laboratory and clinical combined, and must be conducted in a public institution.

4.—The reports must be **(a)** designated by a distinctive word or motto, and **(b)** must be accompanied by a sealed envelope marked with the said word or motto, and containing the name and address of the competitor and of the laboratories or hospitals in which the research was conducted. **(c)** The report and protocol must be typewritten. **(d)** These must be in the hands of the Chairman of the Committee before April 1, 1913.

5.—The reports and protocols are to be judged by a Committee consisting of the three Vice-Presidents of the Society, who shall decide which are the best reports as showing valuable therapeutic research, and shall return their decision, together with all the papers submitted to them, to the Chairman of the Council of the Society before May 1, 1913.

6.—The Chairman of the Council shall then return the unsuccessful reports to their authors, and shall notify the successful author or authors.

7.—The successful report or reports shall be read by the author, or a designated member of the Society, on the first day of the meeting of the Society, immediately after the President's address.

8.—All matters connected with the competition shall be considered as absolutely confidential by the Chairman of the Council and the Judges, except as to the successful competitors.

9.—The Vice-Presidents as judges may fail to award any prize if the report or reports entered in the contest are not found to be of a sufficiently high standard.

10.—In case any Vice-President shall fail to act, the President of the Society shall designate a substitute.

Reynold Webb Wilcox.
Thomas L. Satterthwaite,
Spencer L. Dawes,
Committee on Prize Competition in Therapeutic Research.

PAPERS READ BEFORE THE SOCIETY.*

Anders, J. M.—What Constitutes a Useful Drug, and Shall the Preparations of a Useful Drug be Limited to One or Two? Read by title (1910). (*Monthly Cyclopedia and Medical Bulletin*, Feb., 1911.) Obituary of Dr. J. V. Shoemaker (1911). Dioxydiamidoarsenobenzol in the Treatment of Various Clinical Forms of Syphilis. (*Monthly Cyclopedia and Medical Bulletin*, July, 1912.)

Babcock, W. W.—The Range of Activity and the Untoward Effects of Certain Spinal Analgesics; Based on Two Thousand Administrations (1910). Uses and Limitations of General Anesthesia as Produced by Subcutaneous and Intravascular Injections. (*Monthly Cyclopedia and Medical Bulletin*, Jan., 1912.) The Treatment of Somatic Death. (*Monthly Cyclopedia and Medical Bulletin*, Dec., 1912.)

Barnes, N. P.—Bacterins: their Present Status in Therapeutics (1910). Filariasis: Report of Case Treated with Dioxydiamidoarsenobenzol. (*Monthly Cyclopedia and Medical Bulletin*, Jan., 1913.)

Barton, W. M.—Hexamethylenamine in the Treatment of Otitis Media (1910).

Beates, Jr., H.—Some Fundamental Principles in Digitalis Therapy. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, Sept., 1912.)

Beck, C.—On Morbus Basedowi. Read by title (1910).

Beebe, S. P.—The Preparation of Thyroid Gland for Use (1910).

Blackader, A. D.—Presidential Address, 1912. (*Monthly Cyclopedia and Medical Bulletin*, Aug., 1912.)

Blake, C. J.—Obituary of Dr. Louis Nelson (1912).

Boos, W. F.—The Newer Heart Remedies (1911).

Brown, P. K.—A Modified Vaccine Therapy in Pneumonia; with Animal Experiments (1911).

Cohen, S. S.—What Unofficial Drugs are of Sufficient Clinical Value to be Recognized in the United States Pharmacopœia of 1910? Read by title (1910).

Croftan, A. C.—The Nature of the Cardiovascular Changes in Nephritis. (*Monthly Cyclopedia and Medical Bulletin*, Sept., 1912.)

Crothers, T. D.—The Delusion of the Stimulant and Tonic Effects of Alcohol. (*Monthly Cyclopedia and Medical Bulletin*, July, 1911.)

Da Costa, J. C., Jr.—The Routine Use of the Autogenous Vaccines (Bacterins) in the German Hospital, Philadelphia (1910).

Davis, N. S., Jr.—Should the Pharmacopœia Contain Only Useful and Efficient Drugs? (*Monthly Cyclopedia and Medical Bulletin*, Feb., 1911.)

Dawes, S. L.—The General Treatment of High Blood-pressure. (*Monthly Cyclopedia and Medical Bulletin*, Dec., 1912.)

Evans, D. J.—High Blood-pressure in the Toxemias of Pregnancy. (*Monthly Cyclopedia and Medical Bulletin*, Nov., 1912.)

Fisher, E. D.—Senile Epilepsy. (*Monthly Cyclopedia and Medical Bulletin*, September, 1910.) General Paresis, Tabes, and Cerebrospinal Syphilis. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, 1912.) High Blood-pressure Arising from Nervous Strain in Diseases of the Nervous System. (*Monthly Cyclopedia and Medical Bulletin*, Oct., 1912.)

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* For list of papers read before the Society from its organization to the year 1909, inclusive, see the *Transactions* for 1909.

FLICK, L. F.—Skin Inunctions as a Therapeutic Measure. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, Aug., 1910.)

FUSSELL, M. H.—Further Consideration of the United States Pharmacopœia. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, March, 1911.) Obituary of Dr. John H. Musser (1912).

GALLANT, A. E.—The Delayed Menopause: its Dangers and Therapeutic Indications. (*New York Medical Journal*, June 18, 1910.) Panhysterocolpectomy for Hernia Vaginæ. (*Monthly Cyclopedia and Medical Bulletin*, Dec., 1911.) The Therapeutics of Sacroiliac Relaxation as a Sequel to Surgical Operations. (*Monthly Cyclopedia and Medical Bulletin*, Feb., 1913.)

GOMPERTZ, L. M.—Medical Treatment of Gastric and Duodenal Ulcer. (*Monthly Cyclopedia and Medical Bulletin*, March, 1913.)

GORDINIER, H. C.—Chronic Acetanilide Poisoning a Perfectly Definite Symptom-complex. (*Monthly Cyclopedia and Medical Bulletin*, 1912.)

GREEN, C. L.—Asthenia Universalis Congenita. (*American Journal of the Medical Sciences*, 1910.)

HUGHES, C. H.—Obituary of Dr. Justin Steer (1911).

KEBLER, L. F.—The Present Status of Drug Addictions in the United States. (*Monthly Cyclopedia and Medical Bulletin*, Jan., 1911.)

KING, A.—Further Study of Diabetes as an Infectious Disease. (*Monthly Cyclopedia and Medical Bulletin*, July, 1910.) Diabetes Mellitus from a Surgical Standpoint. (*Monthly Cyclopedia and Medical Bulletin*, Aug., 1911.)

KOLIPINSKI, L.—Further Use of Solution of Calcium Creosote in Medicine. (*Monthly Cyclopedia and Medical Bulletin*, August, 1910.) On the Uses of Nickel Sulphate in Medicine. (*Monthly Cyclopedia and Medical Bulletin*, June, 1911.) The Proper Dietetic Treatment of Diabetes Mellitus. (*Monthly Cyclopedia and Medical Bulletin*, Aug. and Sept., 1912.)

LARRABEE, R. C.—The Treatment of Leukemia with the Mixed Toxins of Coley (1911).

LEECH, D. O.—Obituary of Dr. H. H. Barker (1911).

LONG, E. H.—The Metric System. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, Mar., 1911.)

MCPHEDRAN, A.—Treatment of Pneumonia. (*Monthly Cyclopedia and Medical Bulletin*, June, 1910.)

MORGAN, F. P.—Suggestions for the Pharmacopœia of 1910: A Brief Consideration of the Subject in its Relation to the Federal Food and Drugs Act. (*Monthly Cyclopedia and Medical Bulletin*, March, 1911.)

MORRIS, R. T.—Surgery of the Obese. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, 1910.) Epithelial Conductors and Obstructors. (*Monthly Cyclopedia and Medical Bulletin*, Aug., 1911.)

MORTON, W. G.—Note on Fluorescence Excited Within Human Tissues as a Method of Treatment. (*Monthly Cyclopedia and Medical Bulletin*, Nov., 1911.)

NAGLE, E. W.—Some Observations on Vaccine Therapy. (*Monthly Cyclopedia and Medical Bulletin*, June, 1911.)

OSBORNE, O. T.—U. S. P., 1910. How May It Be Constructed? (*Monthly Cyclopedia and Medical Bulletin*, Jan., 1911.) Common Types of Thyroid Hyposecretion. (*Journal of American Medical Association*, 1912.)

PORTER, W. H.—Sodium Nitrite in Arterial Hypertension. (*Monthly Cyclopedia and Medical Bulletin*, Feb., 1913.)

POTTENGER, F. M.—Some of the Factors which Alter Blood-pressure in Pulmonary Tuberculosis. (*Monthly Cyclopedia and Medical Bulletin*, Oct., 1912.)

REMINGTON, J. P.—Revision of the United States Pharmacopœia. (*Monthly Cyclopedia and Medical Bulletin*, Feb., 1911.)

Ross, George G.—A Case of Recurrent Abscess Formation, Due to Staphylococcus Infection, Successfully Treated by Autogenous Vaccines. Read by title. (*Monthly Cyclopedia and Medical Bulletin*, September, 1910.)

Rudolf, R. D.—Effects of Medicinal Doses of Aconite upon the Pulse Rate. Read by title. (*American Journal of the Medical Sciences*, Dec., 1912.)

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McGILL UNIVERSITY AND ITS MEDICAL DEPARTMENT.

McGill University, under whose auspices the thirteenth annual meeting of the American Therapeutic Society was held, was founded, as stated by the President in his address, by Mr. James McGill, a wealthy merchant of Montreal, who at his death, in 1813, left his fortune for that purpose. The history of the Medical Faculty of the University is closely linked with that of the Montreal General Hospital and the beginnings of medical education in Canada. The five founders of the General Hospital established at the same time the "Montreal Medical Institute," in a small frame building on the site now occupied by the Bank of Montreal; and in 1824 25 students assembled to receive the first course of medical training given in Canada. After continuing as an independent enterprise for four years, the Montreal Medical Institute, owing largely to the exertions of Dr. Stevenson, one of these founders, became the Faculty of Medicine of McGill University, and so prevented the lapse of the McGill bequest to the residuary legatees, the Des Rivieres family. Thus, in all probability, the Medical Faculty was the means of keeping the University in existence, while, through the sound training given its graduates in medicine, it maintained for many succeeding decades the institution's reputation as a seat of learning. For some years the medical instruction was carried on in the top floor of the Central Arts Building, but, this being found too inconvenient of access, Dr. Campbell and other members of the Faculty built a new Medical School in Cote Street, adjoining the Theatre Royal. This was occupied from 1853 to 1872, when a substantial cut-stone building was erected by the Governors of the University on the University grounds.

Until 1885 this latter building sufficed for the highest requirements of the medical education of that period. Then, however, the necessity for further extension of laboratory teaching required an addition to the structure, and from that time on various additions and improvements were made, until, with the gift of $100,000 from the family of Lord Strathcona in 1898, the Faculty, soon after the beginning of the new century, were enabled to provide ample room and the most modern equipment for the conduct of laboratory and didactic teaching of 200 students, as well as ample museum and library space. This extensive and complete building had been in use scarcely five years when the disastrous fire of April, 1907, entirely destroyed the central building and a large portion of the front wing (the original medical building) and greatly damaged the laboratory wing. This fire completely destroyed the departments of anatomy and pathology, with the libraries, specimens, and anatomical collections connected with them, as well as the museum of obstetrics and gynecology.

The laboratory wing was restored and so modified as to contain the necessary equipment for all departments in time for the opening of the session of 1907-08, and lectures were given at various University buildings and in the hospitals. Lord Strathcona presented a site for a new building at the northern end of the University grounds, opposite the Royal Victoria Hospital, and competitive designs for its construction were promptly invited. Later (in June, 1909) the same generous benefactor came forward with a gift of $450,000, which enabled the University to complete and equip the whole building according to the original plans. This beautiful and commodious new home of the Medical Faculty, which is of finely cut Montreal limestone and has a frontage of 268 feet on the University campus, was formally opened by His Excellency, Earl Grey, when Governor-general of Canada. Lord Strathcona, by this his latest and most munificent gift to the University, has, in buildings and equipment, placed the McGill Medical Faculty in the foremost position among the medical schools on this Continent.

SCIENTIFIC PROCEEDINGS.*

THIRTEENTH ANNUAL MEETING,

Held under the Auspices of McGill University at Montreal, Canada, May 31 and June 1, 1912.

PRESIDENTIAL ADDRESS.

By ALEXANDER D. BLACKADER, M.D.,
Professor of Therapeutics in McGill University,
MONTREAL, CANADA.

Members of the American Therapeutic Society:—

In opening the Thirteenth Annual Meeting of our Society my first duty is to thank you for the honor you have conferred upon me in electing me as your presiding officer for the society year which is so shortly to close. Appreciating the honor deeply, it has been my endeavor to make this meeting as interesting and profitable as possible, although I am conscious that it will by no means reach the high-water mark of some of your previous meetings; I allude more particularly to those in New Haven, in Washington, and in Philadelphia.

In making the arrangements for the program I have had willing and able assistance rendered by all the members of the Program Committee, and by our very able Secretary. To each individually I tender my thanks.

It is also my privilege to welcome the Society to Montreal. On behalf of our university, our profession, and of the citizens generally, I bid you welcome to this city, the largest and most prosperous in our Dominion.

As you may have noted, Montreal is delightfully situated on an island lying at the junction of the two noble rivers, the St. Lawrence and the Ottawa. In 1535, Jacques Cartier first sailed up the river and landed on our shores, and after climbing to the top bestowed upon the mountain the name of "Mont Real." It was not, however, until 1642 that Montreal was definitely founded by Paul de Chomedy, Sieur de Maisonneuve, at the head of a band of enthusiasts, who conferred upon their settlement the name of "Ville Marie." As the name implied, theirs was a religious undertaking, and was an attempt to found in America a veritable Kingdom of God; its incep-

* It is to be understood that the Society does not hold itself responsible for any views expressed by the readers of papers or participants in discussions.

tion was stimulated by stories of heavenly voices, of divine revelations, and providential occurrences. For many years, however, the founders had need of all their enthusiasm, faith, and personal energy in repelling the attacks of the powerful Iroquois Indians who surrounded them. Perhaps no other city in America can boast of so many stories of romance and heroism, many of which are told in a most charming way by your delightful writer, Dr. Parkman. For more than one hundred years the city was a stronghold of the French colonists and grew rapidly in size and importance, becoming the center of the profitable fur trade with the northwest. It was the post also from which many hostile expeditions were sent out against both the English colonies on the south and their cruel allies, the Iroquois, to the west and southwest. It was from Montreal, also, that Joliet, Marquette, Du Lhut, Hennepin, La Salle, and many others started on their adventurous careers for the exploration of the western rivers and wilds of your country.

In 1760, the year after the fall of Quebec, Montreal was captured by the English, and Canada became a British possession. Sixteen years later, during the winter of 1776 to 1777, it was occupied by General Montgomery, of the then Revolutionary Army, and during that year Benjamin Franklin, residing in the building which still stands on Jacques Cartier Square and is known as the "Château de Ramezay," in vain endeavored to persuade the Canadians to join in the American revolt against England. The following summer, however, again saw the British flag floating over the citadel of Montreal. For the next twenty years the city was the scene of many conflicts and much romantic adventure owing to the furious contests between the northwest traders and the Hudson's Bay Company. After the fusion, or merger as it is now called, of these rival companies, conditions became more settled and the city became the entrepôt for all the fur trade of both the northwest and the region surrounding Hudson's Bay. Here the merchants associated with this trade lived as princes and spent their profits in generous hospitality, and their names still survive in many of our squares and streets. One of them, Mr. James McGill, who died in 1813, left all his property, valued at the time at thirty thousand pounds sterling, for the foundation of an institution of learning to be called by his name. It is under the auspices of the university founded by him that you meet today.

As stated in our Constitution, the object of our Society is the promotion of therapeutics, a term which may be made to cover the whole of medicine. Therapeusis, the cure of disease, is the end of all medical study, and the term used in this broad sense embraces all means which have to do with the saving of life, the relief of suffering, and the conservation of human energy. It thus may include remedial measures of all kinds—hygienic, dietetic, psychotherapeutic, climatic, hydrotherapeutic, and gymnastic—and all knowledge which may lead up to the proper application of these measures to the individual case. It may also embrace surgery itself. Under such a definition our Society embraces all medicine.

Employing the term in the more limited meaning under which it is generally understood, namely, that department of medicine which has to do

with remedial drugs and remedial measures, as differentiated from those branches of medicine which have to deal with the study of the causes of disease and with its diagnosis and prevention, I have asked myself whether therapeutics today takes the place which it surely ought to hold in medical teaching and in advanced medical thought. To many it appears to fail in doing so. There are few of our great internists who have not for many past decades been more or less permeated with "Osler's black, helpless, hopeless, therapeutic pessimism." It is only recently that an eminent American pharmacologist wrote as follows: "A generation ago therapeutics was an art, promising to develop into a science. At present it cannot be classed as an art, certainly not as a science; it can only be regarded as a confusion." In a recent work by an English physician I read as follows: "Although surgery during the last fifty years has been advancing by leaps and bounds, general medicine has been standing comparatively still. When it has moved at all it has been chiefly on the lines of elucidating the causes of disease, of improving our methods of diagnosis, of discovering new means for its prevention. As regards treatment, it has remained very nearly as empirical as it was a century ago. Perhaps this is rather a hard saying, but in the main it is a true one." That there have been many changes, however, is apparent to all.

Will you pardon a personal reminiscence of the various phases in treatment which have taken place since I was a student in the late sixties of last century and listened to the lectures of my most revered teacher, Dr. R. Palmer Howard, than whom few teachers had a clearer mind, or a greater faith in the value of drug therapeutics. I can recall the numerous instances in which bleeding was recommended, although perhaps with some hesitancy; the frequency with which mercury was ordered in many inflammatory conditions until the gums were touched, and the confidence with which tartar emetic was given in the early treatment of pneumonia. I have a vivid recollection, some years later, of pouring over the pages of my Ziemmsen by night, reading the enthusiastic Liebermeister, and dosing my toxic patients on the following day with 20 or 30 grains of quinine, given two and three times a day, in the vain hope of lowering temperature and antagonizing the infection. I have sat up on many occasions all night at the crisis of a pneumonia, administering alcohol with a very free hand, so that but little was left in the bottle of brandy by the morning; and it was but yesterday that I have plunged my typhoid patients, to quote Osler, "sizzling hot, into a bath of iced water, for a quarter of an hour at a time, and watched them, all cyanosed, shiver and chatter in a vain attempt to regain at least comfort."

It is seldom that any of these treatments are carried out in their entirety today. As for tomorrow—well! there are those who claim that the methods of therapeutics, like the fashions, return in cycles. I often wonder what my students forty years hereafter will think of the prescriptions I now recommend them. And the results in the past and in the present? With a few notable exceptions, not very different.

Indeed, it must be recognized that among the hundreds of drugs in our Pharmacopœia and Dispensatories the drugs that cure—our specific remedies—may be counted on our fingers, and some physicians would even say, on the

fingers of one hand. All the others assist us only in the relief of symptoms; too often with this symptomatic treatment the physician trusts to nature, and plays to the gallery.

And, in trusting to this *vis medicatrix naturæ*, what a wonderful revelation of her powers in combating disease has been made to us by the studies of Metchnikoff, Ehrlich, Morgenroth, Wassermann, Wright, and many others! How dimly have we up to the present appreciated the fact that there resides within the animal body a set of potential forces, capable when aroused and stimulated of exercising a highly effective control over almost all forms of disease! In common with the rest of the medical world we are amazed at the marvelously perfect means possessed by nature, under favorable circumstances, for the destruction of the damaging agent and for the restoration of the damages wrought by disease. Ehrlich writes: "Nature provides in the most perfect manner charmed bullets which strike only those objects for whose destruction the organism has produced them."

Is there a more interesting story written than the description by Ehrlich of the struggle between the invading parasites and their unfortunate host; of the parasites with their toxins, their mutations, and their dodging into dark and hidden places to avoid attack, and, on the other hand, of the gradual development of defensive powers by the host, till finally, by means of his phagocytes, his antitoxins and antiendotoxins, his amboceptors, his agglutinins, and, lastly, by his opsonins, he attacks, and, given a fair fighting chance, defeats, the invaders? In a small percentage of cases only is he in the end himself overcome.

The investigations that have been carried on along this line of thought during the past decade have demanded and will demand the co-operative action of many observers. In the elucidation of these mysteries of nature the general practitioner has but a small place. Such investigations require time, a perfection of laboratory resources, the permission to experiment upon the lower animals, and, most important of all, enthusiastic master minds open to all the whisperings of nature. As a rule they can be carried on only in institutions or colleges endowed by governments, as in Germany, or by generous private individuals, of whom America contains so many notable examples. May the day for Canada soon arise when her rich philanthropists will consider that in no worthier way can their money be spent than in the elucidation of the mysteries which still enshroud our knowledge of the conditions under which we suffer, live, and die.

Our belief is that in strengthening this wonderful mechanism of nature lies the therapy of the future; but there is still an infinity to be learned, for the mysteries of the antibodies have as yet scarcely been fringed. It was a great disappointment to our rising enthusiasm when Sir Almroth Wright's too hopeful statements regarding the opsonins appeared to fail. To obtain by a culture-growth knowledge of the precise organism that is causing a patient's malady, and to learn by examination of the blood the exact condition of the antagonizing power in that patient's blood-cells and serum, and with the knowledge so obtained to work along nature's lines, reinforcing the resisting

powers and checking the development of the infecting organism, is "a consummation devoutly to be wished."

In connection with these thoughts let me remind you that no advance in therapeutics has been of greater value to the world than the modern appreciation by physicians, and, altogether too slowly, by the general public, of the advantages accruing from the breathing of fresh air, of sleeping in it, working in it, and as far as possible of living in the open. It is undoubtedly one of the greatest stimulants to the activities of the phagocytes and to the development of the various forms of antibodies that the physician today possesses. Doubtless also, the great value of climatotherapy, of hydrotherapy, of psychotherapy, and possibly also of electrotherapy depends on a similar stimulation of this wonderful defensive mechanism of nature. Bier's method for the induction of local hyperemia likewise affords the physician a means for the reinforcement of these natural forces at any desired spot.

Much valuable thought along these lines has also been given to the profession by our respected confrère, Dr. Sajous, who in his philosophical presentation of the action of the adrenal, the thyroid, and the pituitary glands has told us of the active part which he believes they take in the development of these antibodies. The profession all over the world places a high estimate on the researches which his enthusiasm and his unflagging energy have carried out in connection with the various activities of these internal secretions, and we hope to hear still further from him at our present meeting.

But although I speak in this strain, I am by no means willing to be classed as a hopeless pessimist regarding the value of drug therapy. On the contrary, I have a strong belief in the limited value of the great majority of our pharmacopeial drugs when used with a definite knowledge of their action; of what they can do, and what they cannot do; of the lines in which they may help, and of the many ways in which they can harm. Only when we know the exact physiological action of a drug, both in health and under pathological conditions, are we able to use that drug in a useful, purposeful way and to avoid its undesired and too often toxic side-effects.

The outlook in therapeutics has been dark because hitherto therapeutics has been taught as a mere empiricism. The future is bright because in all our best medical institutions of learning the students today are taught practically, as well as theoretically, the action of each drug. No man who has observed the definite action of a drug in his laboratory is likely to develop into an agnostic in therapeutics, and it is my belief that, if the many brilliant internists who at the present are therapeutic pessimists had had the advantage of a practical training in a modern pharmacological laboratory during their student days, they would now speak with a clearer, and frequently with a more optimistic, note in reference to therapeutics.

During the past year therapeutists have been greatly encouraged by the success which has attended Ehrlich's persevering investigations into the modifications of therapeutic action by variations in chemical structure. Animated by the belief that pharmacological action is dependent upon the relative affinities between the cells and tissues and the drug, an affinity which determines its distribution in the system and the special cells to be brought under its influence.

he finally demonstrated that these affinities may be altered by variations in chemical structure often of a slight character.

The story of the confident steadfastness with which he carried out his investigations, even from the time of his student days, is a record of wonderful perseverance. Thousands of substances had to be examined by chemical and animal experimentation. He tells us that he himself examined over 600. Now all the medical world is aware of and rejoices in his final success.

A similar investigation is now being carried on in the Rockefeller Institute, where Flexner is endeavoring to elaborate some modification of hexamethylenamine which, while retaining its central formation with its effective germicidal action, may develop a specific affinity for, and a toxic action on, the micro-organisms of poliomyelitis.

Success will doubtless come with time, for it is our confident belief that increasing knowledge of the subtleties of chemistry will in the not distant future provide the physician with many drugs having a specific action on certain forms of disease, and thus enable him to gain the victory, or greatly assist the powers of nature in overcoming the disease.

In anticipation of this time, however, there has arisen an impatient demand among physicians for new remedial agents, and as a result numberless commercial houses are foisting upon the profession an enormous array of new drugs with catchy and therapeutically suggestive names. Of these a few may have some value; the majority unfortunately have little or none, and some appear to be distinctly harmful. Of the exact action of these drugs for good or evil we have no knowledge except the statements of the commercial houses introducing them, which are invariably much prejudiced. Many of the new drugs introduced, even by reputable houses, have been shown by analysis to have a composition differing greatly from that stated. It appears to me therefore to be of the utmost importance that physicians should accept all unproved statements very cautiously, and should for the present rely almost entirely on the standard preparations of their Pharmacopœia, of which they know the exact composition and physiological action.

In the detection of the false and the uncovering of wrong, the work done by the Council on Pharmacy and Chemistry of the American Medical Association has been of the greatest value. All honor to the men who so nobly carry on this work without remuneration and in such an unostentatious way!

Let me say here how highly the profession in Canada appreciates this work and the proposition of this Council to institute a critical study of many of the more important problems in therapeutics demanding investigation. It is stated that a compilation will be made of all available data and supplied to all members of our profession who will assist the work with careful clinical research. Later on, digests and monographs will be furnished giving the results of this work, and these will supply the profession with facts upon which dependence can be placed.

Such an effort should have not only our good wishes, but our active co-operation. In my opinion this Society should take a prominent part in all such investigations.

OBITUARIES.

CARL BECK, M.D.

By REYNOLD WEBB WILCOX, M.D.,

NEW YORK CITY.

Carl Beck was born in Neckargemund, Germany, on April 4, 1856, and died at his country residence in Pelham, New York, on June 8, 1911. His university education was received at Heidelberg, Berlin, and Jena, which conferred upon him the degree of Doctor of Medicine in 1879. On coming to this country he at once chose surgery as his special work and won a distinction, which was well merited, for diagnostic skill and ability to operate so that success in an eminent degree marked his work. His hospital work was mostly done at the German Poliklinik, at the New York Post-Graduate Medical School and Hospital, which elected him Professor of Surgery in 1890, and at St. Mark's Hospital, where he was appointed Surgeon in 1886. At St. Mark's Hospital he built up one of the largest surgical clinics in this country, and here he acquired an enormous experience, which he freely utilized for his books and for his teaching. Through his wide acquaintance with foreign surgeons and especially those of Germany, and which was maintained through his yearly vacations spent in the fatherland, St. Mark's Hospital is probably the best known of all American hospitals, and the leading German surgeons always visit it when in this country. As Corresponding Member of the Muenchener Medizinische Gesellschaft and of the Hungarian Medical Society, much of his work has been communicated to the profession in Germany and Austria-Hungary. In this country, he was President of this Society in 1905-6, and also served in the same capacity in the Society of Medical Jurisprudence and in the German Medical Society. He received the Nicholas Senn medal, and in 1908 was made Knight of the North Star by the King of Sweden.

So soon as the discoveries of Roentgen were announced, he saw the possibilities which presented themselves, and immediately installed a plant and was the first of American surgeons to utilize this method of investigation in his daily work. His works, "The Use of the Roentgen Rays in Surgery" and "Roentgen Ray Diagnosis and Therapy," are standard today, as they were pioneer at the time of their appearance. He also wrote two other books, "Surgical Asepsis" and "Diseases of the Chest," from the surgical viewpoint, and, in addition, about one hundred monographs on various surgical subjects. As a surgeon he was technically aseptic, fearless in conception, and rapid in execution. The amount of work which he did was enormous, and to this was added a vast amount of executive detail which his various positions

brought to him, so that finally his vigorous physique succumbed to the overwhelming load.

Nor were his activities confined to surgery. He was the founder and for many years President of the Vereinigung Alter Deutscher Studenten in Amerika, in which he gathered together the best of those whose education had been wholly or in part obtained in German universities. He wrote also "Der Schwedenkonrad," "Feuchtfroeliches und Unfeuchtfroeliches," and "In Lateinischen Amerika," which are examples of his lighter vein.

This is the record of Carl Beck's notable public career and his more prominent achievements. In his far too short life he accomplished much that has been for the betterment of surgery and for the lasting benefit of mankind.

To those of us who are permitted to know the man from our old days together in Heidelberg, through the storm and stress of constructive work in medicine and surgery in this country, in the festive days of student or medical associations, in the quieter home or club circle, his going from us is overwhelming. As a surgeon, he had attained eminence in the world; as a colleague and friend, he was supreme in our affection.

679 Madison Ave., New York.

JOHN HERR MUSSER, M.D.

By M. HOWARD FUSSELL, M.D.,

PHILADELPHIA, PA.

To call to notice the date of birth of this great man and the various positions he has held would be to note only what is written in almost every newspaper of the country, and which will go down to posterity in the ordinary biographies and Encyclopedias.

To say—Student of Medicine at the University of Pennsylvania; Interne at Blockley; Physician to the Out-patient Department of the University of Pennsylvania; Assistant Professor of Medicine; Professor of Clinical Medicine; Author; President of the American Medical Association; Public Servant; Consultant; Practitioner of Medicine, calls to mind the steady rise of this youth, young man, mature individual, but does scarcely more; many men have done like deeds. To appreciate the greatness of the man, this skeleton of his career must be analyzed.

As a student of medicine he was zealous to learn all that was possible of the great subject that was to be his lifework. In Blockley he was one of the best of Resident Physicians, kind to his patients, polite to his superiors, indefatigable in his work.

As a teacher of medicine he impressed his students and colleagues with his thoroughness, his untiring industry, his wide knowledge, his great desire to help those who came under his care.

His prominence, already great, was much increased by his elevation to the Presidency of the American Medical Association. In this position he showed his ability to organize and his grasp of the fundamentals so necessary to the correct method of conducting an organization so vast as the Association is proving itself to be. Dr. Musser's grasp of public ideals, his sterling independence, was shown in his attitude in the later movements for reform government in Philadelphia. Notwithstanding his overbusy professional life, he took time to take personal interest in the movement for good government, to help organize and to encourage his fellow-practitioners in that work. This notwithstanding the fact that some of his most intimate personal friends were opposed to his views. He was frequently called upon by the Government for expert opinions on subjects germane to his lifework.

Dr. Musser's titles are very numerous. Among the most noteworthy is his book on Physical Diagnosis and his Treatment, written in conjunction with the lamented Kelly. All these things other men have done, but it is the influence John Musser exercised as practitioner of medicine, hospital physician, and consultant which will cause his name to be held in loving remembrance by those who came in personal contact with him, while generations to come will be influenced by his great achievements in this part of his career.

He will forever keep company with such men as Agnew and Flint.

As a practitioner and consultant he was at his best. His private patients and those who had his help as a consultant were devoted to him. His bright, cheery way, as much as his intimate knowledge of their condition, helped many to recovery, and consoled and made happy those for whom there was no earthly help.

During the very last years of his life, when reputation and affluence were his, he organized a social-service work at the University of Pennsylvania which is doing more to make fruitful the technical work of the hospital than any one thing that has occurred in the career of that institution.

And so, though always Musser will be remembered as a Great Clinician, he will be enthroned in the minds of those who come after as Doctor, Helper, Friend.

LOUIS NELSON, A.M., M.D.

By CLARENCE JOHN BLAKE, M.D.,

BOSTON, MASS.

Dr. Nelson was born in Boston, Mass., July 5, 1878. He attended the public schools and prepared for college in the English High School of Boston; entered Harvard in 1896, and received his Bachelor's Degree with the class of 1900.

Having decided to take up the study of medicine, he matriculated in the Harvard Medical School and graduated with honors in 1904.

In the autumn of the same year he returned to the Medical School for postgraduate work and devoted his time to special study and research.

As a reward for his endeavors he received his Master's Degree in Arts the following June, and incidentally won the Boylston medical prize.

Dr. Nelson was appointed assistant in the Department of Pharmacology at Harvard in June, 1906, but after finishing one year of service declined reappointment and went to Europe for further study. He settled in the University of Strasburg and remained there for two years, becoming assistant to Professor Schmiedeberg.

Soon after returning to his native city Dr. Nelson opened an office in Boston and began to practise his chosen profession, at the same time continuing his scientific investigations.

In September, 1909, he was made Instructor in Pharmacology in the Harvard Medical School, and was actively connected with the school in the same capacity up to the time of his death.

Dr. Nelson has written a number of articles, both in German and English, setting forth the results of original research.

The unexpected termination of a brief illness came as a shock to all who knew him.

Endowed by nature with a frank, likable personality, he made and held many friends, and the same qualities brought him success in the lecture room.

His sympathetic and generous consideration for the people who sought his advice or services had already begun to reap its reward in the shape of a steadily increasing practice.

Death in the midst of activity is a sad bereavement and this was especially true in the departure from life of our much esteemed friend. Dr. Nelson was scarcely more than upon the threshold of a career full of promise, with youth, unusual training, and attributes essential to success at his command, when he was suddenly taken from us by the hand of death.

When in the passage of time the grief of relatives and friends becomes merged in resignation, we find a recompense in the appreciation of the fact that the sunshine he scattered upon the highway of life will not be soon forgotten and the place he won in the hearts of those who knew him will endure.

Dr. C. E. de M. Sajous, of Philadelphia, said he was sure that all who were at the Boston meeting, in 1911, would hold in grateful remembrance the young physician who so ably assisted Dr. Blake in his arrangements for the Society, and who, in particular, did so much for the pleasure and comfort of the members when they visited the Pharmacological Department of the Harvard Medical School.

HENRY ALFRED ROBBINS, M.D.

By J. W. CHAPPELL, M.D.,
WASHINGTON, D. C.

Dr. Henry A. Robbins was born in St. Louis, Mo., in the year 1839. His father, Zenas Robbins, moved to this city on being appointed, by President Lincoln, Register of Wills for the District of Columbia. Dr. Robbins was educated in the schools of Washington and at Norwich University. He subsequently attended lectures in the Medical Department of the University of Pennsylvania, graduating in 1861. At the outbreak of the Civil War he enlisted in the Union Army as a medical cadet, with the rank of assistant surgeon, and served faithfully through the whole conflict. At the close of the war President Lincoln tendered him a commission in the regular army, which he declined, preferring to practise medicine in civil life. The Doctor also spent a number of years in Europe perfecting himself in medicine by attending numerous courses of lectures and clinics in the leading universities and hospitals of London, Berlin, and Vienna.

He arrived in Paris at the time of the Commune and rendered very efficient service as a regular army surgeon during a large part of that turbulent period.

He practised his profession in Washington for many years, also filling a chair as professor and lecturer in several of the schools of the city. He was a constant contributor to many of the leading medical periodicals and read from time to time many interesting and instructive papers before various medical societies of the District.

He was noted for his zeal in research in medical literature and was a recognized authority on a number of important subjects.

He was a member of the Medical Society of the District of Columbia, being at one time one of its Vice-Presidents; he was a member of the Medical Association of the District of Columbia, a member of the American Medical Association, a member of the American Therapeutic Society, and a member of other medical bodies and scientific organizations. He was also a member of the Sons of the American Revolution, a member of the Union Soldiers' Alliance, and a member of Kit Carson Post, G. A. R., Department of the Potomac, and was prominent and took an active part in Masonic affairs; being a 32d degree Mason and a member of Hiram Chapter, No. 10, F. H. A. M. He also took much interest in the Scottish Rite, Mystic Shrine, and the Blue Lodge. He was also a member of the University Club and a member of the Alumni Association of the University of Pennsylvania, of which he was a former President.

It is with profound sorrow that the members of the American Therapeutic Society hear of the death of Dr. Robbins, who was an active and an enthusiastic member and a genial gentleman. Dr. Henry A. Robbins departed this life October 26, 1911, at his residence, 1750 M Street, N. W., in the

72d year of his age, his death being due to his advanced years and a complication of diseases.

Dr. Robbins leaves a wife and a son, Lieutenant Alfred McCallum Robbins, U. S. A.

Now, therefore, be it resolved, that the American Therapeutic Society, feeling deeply the loss it has sustained, tender its heartfelt sympathy to the family of Dr. Henry A. Robbins in this their sorrowful hour, and record this resolution as an evidence of its appreciation of his noble character and professional worth.

This resolution was, on motion, adopted by the Society.

THE TREATMENT OF SOMATIC DEATH.

By W. WAYNE BABCOCK, M.D.,

Professor of Surgery in the Medical Department of Temple University;
Surgeon to the Samaritan Hospital,

PHILADELPHIA, PA.

Legally a man is considered to be dead when a qualified physician, upon examination, pronounces him so to be. For centuries physicians have based their concepts of death upon the cessation of the so-called vital activities. When evidence of respiration, circulation, and cerebration may no longer be detected, the patient is said to have undergone somatic death. Often with the abolition of the respiration, usually with the cessation of the pulse, the patient is pronounced dead, and the body is permitted to pass from the province of the physician, although it has long been recognized that many cells continue alive and that complete molecular death has not yet occurred throughout the body. The epithelial cells, and epithelial appendages such as the hair, nails, and teeth, may continue to be alive for weeks. The simpler connective tissues, such as bone, cartilage, fibroconnective tissue, in part may continue in a living condition for days; muscles and certain glands live for hours after somatic activities have ceased, while the very highly specialized tissues, particularly of the nervous system, may continue in a living condition for at least a number of minutes after death is supposed to have taken place. Crile's experiments upon dogs show that it is possible to resuscitate these animals after they have been somatically dead for periods of time up to seven and one-half minutes. The cessation of the circulation apparently produces in the neurocytes chromolytic and fiber degeneration, in some places suggesting absolute cellular death. Despite these severe degenerative changes the dog may appear to be well. Thus one animal, that had apparently entirely recovered after seven and one-half minutes of circulatory arrest, was found on *post mortem*, four weeks later, to have a marked degeneration of fibers in the pyramidal fasciculi running from the cord to the cortex and in Flechsig's fasciculi, as well as occasional degenerative changes in other ascending and descending fibers.

As to the period of time that the central nervous system may live after complete arrest of circulation, much remains to be learned. Crile states approximately that the respiratory center may survive anemia thirty to fifty minutes; the vasomotor and cardiac centers, about twenty to thirty minutes; the spinal cord, eight to ten minutes; the motor cortex, eight to ten minutes; the portion of the brain presiding over consciousness, the intellect, and psychic state, six or seven minutes. The higher neurons may live for considerably longer periods than these figures would indicate. In one of my patients certain cord reflexes were regained after not merely ten, but approximately twenty-five, minutes of complete cardiac cessation.

With this knowledge we should abolish the misleading term "somatic death," and should substitute some more exact designation, such as suspended animation. The surgeon, in particular, should be the one who has no belief in somatic death. Many, many persons have passed into molecular death because with the appearance of the signs indicating somatic death the physician has abandoned hope, or has failed persistently to try approved methods of resuscitation. In few operating rooms are the surgeons and attendants drilled in prompt treatment of this so-called death. Remedial methods are usually unsystematic, badly applied, associated frequently with most dangerous delay, and often quickly abandoned. For cardiac failure I have seen half a dozen of surgeons simultaneously produce hypodermic syringes and each proceed to inject into the patient the substance in which he personally had the most faith, irrespective of what was being injected by the others. For respiratory failure, many of you have perhaps seen the harrowing spectacle of two panic-stricken attendants trying independently to practise artificial respiration, the one making inspiratory movements with the one arm at the time expiratory movements were being made by the other, the occluded respiratory passages being in the mean time entirely neglected. It is my belief that in a large proportion of the cases of death from anesthetics resuscitation was possible. It is also my belief that in nearly every case of death under spinal anesthesia the patient might have been resuscitated, provided there had been no advanced organic disease preventing such resuscitation. The cardinal guide in the treatment of these conditions is the *respiratory function*. The most important part in the treatment is the *maintenance of the circulation.*

Perhaps the most powerful and rapidly acting circulatory stimulant at present known is the active principle of the adrenal glands, epinephrin. If it is properly introduced, its effects are prompt; but they are also transient, the duration of the stimulation being about ten or fifteen minutes. The extract of the posterior portion of the pituitary gland has a similar and perhaps a more prolonged action. The adrenal product should be introduced into the circulatory system. Its administration by mouth or subcutaneously is followed by so little systemic effect as to be practically valueless. Its subcutaneous injection may produce extensive, and even very dangerous, local necrosis. *Intravenous injection* is the simplest method for the satisfactory administration of this stimulant. Before every serious operation we have prepared a sterilized six-ounce glass funnel with a hollow needle, connected by six feet of soft-rubber tubing. If the patient shows alarming symptoms, this simple apparatus is filled with warm physiological saline solution and the needle introduced into one of the large veins about the anterior surface of the elbow. Usually the needle may be introduced directly into the vein without an incision of the skin, in which case it may then be strapped to the arm by adhesive plaster, after properly supporting the terminal portion of the rubber tubing and needle. Should there be any difficulty, the vein is exposed and raised upon the finger, and the needle introduced. If the patient's condition is urgent, there should be no hesitation in freely incising the skin and obtaining satisfactory exposure of a large superficial vein. Unfortunately, in an emergency

but few assistants can be depended upon to introduce a needle promptly and accurately into the vessel. Crile's suggestion that the injection should be made into one of the large arteries, so as to flow back and distend the coronaries, involves a more serious procedure, and one that we would not ordinarily commend. The operator is usually so occupied by efforts at artificial respiration, cardiac massage, or other measures that, unless he has an especially well trained staff, he will hesitate, after seeing the usual inefficient efforts at intravenous injection, to order the more difficult and dangerous intra-arterial introduction of the needle. The warm solution having started to run into the vein, and the fact that there is no leakage into the tissues being shown by the absence of local swelling, from 2 to 10 drops of a 1:1000 solution of the epinephrin are to be dropped into the funnel, or, if preferred, injected, as Crile suggests, by a hypodermic needle directly through the wall of the rubber tubing. In human practice often within a few seconds the adrenal effect is perceptible. The color returns to the face and the pulse to the wrists, and the cardiac pulsations grow progressively stronger, so that within a few moments the entire body may be observed to shake from the violence of the circulation and the hand placed upon the operating table may even feel the vibrations from the tremendous cardiac contractions. This extreme violence is undesirable and inflicts a strain upon the circulatory system which may be very harmful. We therefore prefer, unless the patient's condition be unusually urgent, to introduce but 2 or 3 drops of epinephrin into the single funnelful of solution, and as the heart action improves we direct that the tube be pinched so that further entrance of the solution is arrested. Later, if the pulsations weaken, the flow is started and further drops of the stimulant added to the funnel as seems requisite. In this way one may introduce the plain saline solution or a weak or strong solution of the adrenal principle, as required, and the injection may be continued with intermissions for an hour or longer.

In some cases, after cardiac arrest, the solution does not seem properly to enter the cavities of the heart; or the heart has stopped in diastole, and the overdistention must be relieved. Under these circumstances *cardiac massage* is very valuable. Before attempting cardiac massage, however, stimulation of the heart by regular violent blows, made with the ulnar side of the fist, over the precordium, may be tried. If an abdominal incision has been made, the hand is introduced to the diaphragm and the heart rhythmically compressed and massaged against the overlying chest wall. In this way the cavities are largely emptied and a better opportunity for the stimulating solution to enter the heart is obtained. If no abdominal incision has been made, I make a simple stab puncture in the fifth costal interspace, one and one-half inches to the left of the sternum. The index or middle finger is at once pushed through the opening and hooked about the left edge of the heart, which is rhythmically compressed against the overlying chest wall. Leakage of air into the thorax may be prevented by placing wet sterile compresses about the base of the finger, or by employing a small incision. With a very marked dilatation of the heart the compression of a single finger may be insufficient, as illustrated in one of our cases. With an arrested circulation I have been able to produce

by such cardiac massage alone a distinct impulse visible in the vessels of the neck. The period of duration of life after the cessation of cardiac action is still so theoretical, and so based upon experiments on the lower animals, that the attempts at restoring the circulation should be continued for one-half or three-fourths of an hour, or, under certain conditions, even longer.

Of course, the circulation will not continue, even if restored, if there be no respiration, and an important consideration is the *oxygenation of the circulating fluid*. The well-known experiment in which the excised animal heart perfused with Ringer's solution fails and the heart stops beating if the Ringer solution be free from oxygen, suggests that it may be of advantage to pass oxygen through the physiological salt solution before using it. I am indebted to Dr. D. M. Hoyt for this suggestion. In an emergency this may be accomplished by introducing a sterile glass tube to the bottom of the percolator or funnel, so that a stream of oxygen bubbles through the fluid before it enters the vein. The importance of this is emphasized by the fact that the tissues and centers receive their oxygen directly from the plasma, and that the abnormally small oxygen content of the plasma of an asphyxiated person becomes markedly less through the dilution of the plasma with the saline solution.

Artificial respiration, to be efficient, must be given systematically and with careful attention to the patency of the upper respiratory passages. In cases of failing respiration we prove that the air passages are free by keeping a fine wisp of cotton fastened to the tip of the nose. The movements of the cotton serve as a guide, rather than the often-deceptive movements of the chest. Ineffectual methods of artificial respiration are also promptly detected because they fail to move this indicator. One of the simplest and most efficient methods of artificial respiration to be carried out on the operating table is by rhythmic compression of the thorax. The patient's arms are extended above the head, and an assistant holds the patient's head and maintains the freedom of the upper respiratory passages by holding forward the tongue, by elevating the jaw, or by properly extending the head. The folded arms of the surgeons are then placed across the patient's chest, while the assistant, with his hands below the surgeon's elbows, presses upon the lower ribs; the compressions are made downward and inward in such manner as is found to give the greatest range of movement of the wisp of cotton. The extended arms favor the expansion of the chest when the compression is released. In this manner, aided by relays of student assistants, in one case we continued artificial respiration, and so maintained the circulation, for six hours.

Thoracic disease, extreme obesity, marked abdominal enlargement, rigidity of the thoracic walls, or serious intrathoracic disease may prevent the employment of artificial respiration; or the method may interfere with the more urgently needed cardiac massage.

Intratracheal insufflation of oxygen, after the Meltzer-Auer plan, is perhaps the best method at present known. Unfortunately, the introduction of a catheter through the larynx to the tracheal bifurcation may be difficult without a special introducer, which may not be at hand at the unexpected emergency. Having once wasted considerable time in an effort to introduce

a soft and ill-suited catheter through the mouth by finger guidance into the larynx, I have twice since in such an emergency made no effort to introduce the tube by way of the mouth, but have made a small incision through the skin, nicked the trachea, and spread the small opening with a pair of narrow, blunt scissors sufficiently to slip in a small urethral catheter, which was at once connected with the oxygen tank; the catheter used was of small-enough size not to interfere with ordinary respiration or to produce emphysema from excessive oxygen pressure.

During all these procedures the head should be lowered. Not infrequently the heart will start beating solely from the impulse of blood which rushes into it and distends the cavities as the patient's body is inclined.

Summary.—After drowning; after the use of anesthetics; after various forms of asphyxiation, doubtless many hundreds of persons have been considered as dead, and have been permitted to die, because the evidences of somatic death were present. *No physician, particularly no emergency surgeon, should believe in somatic death.* No person should be considered dead until irreparable molecular changes have taken place in vital organs. Cessation of function should no longer be considered as evidence of death. Physicians should be drilled in the technique of resuscitation, and particularly they should be taught as to the need, at times, for long-continued and carefully applied measures. Many persons familiar with surgical technique, quite competent to undertake an appendectomy or herniotomy, are surprisingly inefficient in quickly and accurately giving an intravenous or intra-arterial injection to a dying patient.

The following are illustrative cases:—

CASE I.—*Complete arrest of circulation for about twenty-five minutes and of respiration for about thirty-five minutes. Final resumption of circulation and respiration by cardiac massage, intravenous injections, and forced artificial respiration. Secondary pulmonary edema with death forty-three hours later.*

Mrs. A. D. C., an obese colored woman of 38 years. Nullipara. Ill seventeen years with pain in the right inguinal region, and had noticed progressive abdominal enlargement for fifteen years. No metrorrhagia. The patient entered the Samaritan Hospital December 5, 1911. On the following day she was given $\frac{1}{6}$ gr. of morphine with $\frac{1}{100}$ gr. of scopolamine by hypodermic injection at 2.45 and also at 3.15 P.M. At about 3.52 P.M., as the patient was rapidly becoming stupefied by the narcotic, 5 cg. of alcoholized amylene hydrochloride were injected into the twelfth dorsal interspace. The injection was given in the sitting posture, and, on account of her obesity, there was some delay in placing the patient supine upon the table. About three minutes after the intradural injection a median abdominal incision was made. The blood was very dark and no pulsating vessels were noticed. On examination, it was found that the patient was not breathing, and that the teeth were clenched tightly and the mucous membrane cyanotic. With some delay and difficulty the teeth were pried apart, the tongue pulled forward, and artificial respiration by rhythmic compression of the thorax attempted. These efforts seemed entirely inefficient, the diaphragm being high, the chest short and thick from fat, the abdomen distended and splinted by the large fibroid tumor present, and the neck short and obese, rendering the upper air passages difficult to manipulate. As the patient was pulseless at the wrist, the hand was introduced through the incision, the abdominal aorta grasped, and found also pulseless. Carrying the hand up to the diaphragm, the heart could be felt, apparently rather large and flabby, but without any contractions. Cardiac massage, instituted through the diaphragm, produced no response.

Attempts were again made at artificial respiration, while an assistant endeavored to introduce normal saline solution with epinephrin into a vein of the left arm. After some difficulty it was found that the vein, which was rather collapsed, had not been properly entered, so that the fluid was merely distending the tissues. The assistant was, therefore, directed to try the opposite arm. The patient was now relaxed, the mucous membranes were ashy, the skin was cold, there was no evident reflexes, and every appearance of death was present. An attempt was made to use oxygen through the mouth. Full doses of caffeine and strychnine were injected subcutaneously and, as the efforts at artificial respiration failed to oscillate fibers of cotton fastened in front of the nose and mouth, tracheotomy was rapidly done and a trachea-tube introduced. An effort was then made to inflate the lungs by an intermittent flow of oxygen from the oxygen tank, but the volume of the stream was insufficient. The arms being held above the head, repeated and continued efforts were made to establish respiration by thoracic compression, which was stopped from time to time only long enough to permit the hand to be introduced under the diaphragm, and the heart to be compressed or massaged against the overlying chest wall. Finally, it was observed that the saline solution supposed to be running into the vein of the right arm was dripping from the arm, and in enlarging the incision I found that the vein had been punctured and that the needle lay alongside the vessel. The needle was properly introduced into the vein and the flow of salt solution and epinephrin continued. For perhaps the fifth or sixth time I again introduced the hand and arm into the abdomen and renewed the intermittent compression of the heart, hoping to force out sufficient blood to enable the adrenal product to enter the chambers. The patient had now been apparently dead about twenty-five minutes. Suddenly the hand, grasping the heart, felt a violent and startling thrill, succeeded by rapidly increasing and more violent cardiac contractions. The pulse reappeared at the wrist, the incisions in the arms and abdomen started to bleed, and the ashy color faded from the mucous membrane. The cardiac movements were so violent that the flow of the saline solution containing the adrenal principle was checked. A few minutes later the heart grew weaker, the pulse faded from the wrist, and it was evident that the cardiac action could not continue without efficient respiratory action. The flow of oxygen through the tracheal tube was discontinued and I applied the end of a soft-rubber drainage-tube against the tracheal opening, and blew violently into the lungs. I was gratified to note that the chest expanded and that on the removal of the tube the collapsing chest forced a part of the air out. I continued intermittent insufflation and had the flow of the solution resumed from time to time, as seemed to be required. The pulse now returned and was fairly sustained. An assistant continued the efforts of insufflation. About 4.30 P.M., or about thirty-five minutes after apparent somatic death, the first faint voluntary respiratory movement was observed. Gradually voluntary respiration was resumed. The abdominal incision was closed and the patient returned to her bed with a temperature of 97°, respiratory rate of 24, and pulse of 112. She did not regain consciousness, but winking could be produced by tapping the nose. Some pulmonary edema was evident from the passage of blood and mucus along the tracheal tube. On the day following, the temperature reached 102⅗°. The respiration was more noisy, rapid, and labored, and finally reached 50, while the pulse rose to 160. On the second day at 11.10 A.M., or forty-three hours after the operation, the patient died, the rectal temperature being 107⅗° at the time of death.

CASE II.—*Prolonged artificial respiration, illustrating a remarkable influence of oxygenation upon the circulation.*

A man of good physique, aged about 20, had his left arm avulsed close to the shoulder by a train. He was brought to the operating room about three hours after the accident and observed to be pulseless at the wrist after being placed in a sitting posture upon the operating table. Spinal anesthesia with middorsal injection was given with the hope of blocking shock. At this time we did not realize that an anesthetic increases pre-existing shock, although it may block shock that succeeds its

induction. The patient was placed in a horizontal position and as the stump was being prepared for operation the respiration ceased. Artificial respiration by rhythmic compression of the thorax was at once started, and in about fifteen minutes breathing was resumed, and the circulation had improved. Unwisely, an attempt was then made to trim off the mangled portions of the arm. This was promptly followed by renewed respiratory failure and loss of circulation. Artificial respiration was again started, after which the color returned to the lips and the pulse to the wrist. As there were no voluntary efforts at respiration, and as the patient remained unconscious, artificial respiration was continued by relays of assistants and students. From time to time the efforts at artificial respiration were imperfectly carried out, whereupon the skin would become ashy, while the pulse could no longer be detected at the wrists or over the carotid. By substituting more efficient respiratory movements, the color would return and the pulse reappear. This occurred a number of times. Finally, the cardiac response became feebler, and at last could not be produced. Efforts at artificial respiration lasted from 8 P.M. until about 2 A.M., *i.e.*, circulation was maintained for nearly six hours by artificial respiration.

Not long after this experience, a second young man was admitted with a similar avulsion near the shoulder-joint. He was given no anesthetic or artificial respiration, but was merely given the usual stimulation, a simple occlusive dressing being applied over the wound. This man died of shock about seven hours after admission to the hospital.

CASE III.—*Cardiac and respiratory cessation; illustration of the necessity for efficient cardiac massage.*

Mr. E. H., aged 43, was admitted for advanced and neglected left pyothorax with large subcutaneous phlegmon and right pneumonitis. The patient was in a very bad condition, with pulse of 120 and respiration of 40 on admission. Amylene hydrochloride, 4 cg., was injected through the ninth dorsal interspace at 5.55 P.M. Operative resection of rib at 6 P.M. The opening of the chest was attended by a gush of pus, followed by cardiac and respiratory arrest at 6.02 P.M. Artificial respiration by compression was found to be impossible, and by forced respiration impracticable, because of extensive pulmonary collapse and disease. A stab wound was made through the fifth left intercostal space, with introduction of the finger, which was hooked about the edge of the heart, and rhythmic compressions started. The heart was greatly dilated and the efforts at massage were ineffectual. Salt solution with 20 minims of adrenal blood-pressure-raising principle was introduced into a vein of the arm. As the overdistended heart failed to respond, a second stab puncture was made in the fifth right intercostal space and a second finger introduced. The dilated heart extended nearly from one nipple line to the other. Rhythmic compression and massage by simultaneous flexion movements of the fingers through the two punctures were followed by resumption of cardiac movements after complete cessation of the heart for about ten or fifteen minutes. The heart continued to beat for several minutes, but, as we failed to induce respiratory action, it eventually ceased.

CASE IV.—*Illustrating the futility of efforts at resuscitation with insufficient circulating fluid.*

Mr. X., aged about 45, had swallowed a bone while eating meat four days previously. He entered the hospital for an X-ray picture, and as he started to ascend the stairs he fell over in a faint, with blood gushing from the mouth. The patient was at once brought to the operating room and efforts at resuscitation and cardiac massage made. The rapid leakage from one of the large thoracic vessels, however, rendered all our efforts futile.

CASE V.—*Respiratory and circulatory failure in an aged woman. Successful resuscitation. Death several days later from progressive peritonitis.*

Miss E. H., aged 87. Strangulated umbilical hernia, with peritonitis of two days' standing. Condition bad. Respiration 24 on admission, fecal vomiting; pulse 104.

Para-aminobenzoyldiethylaminoethanol hydrochloride, 9 cg., was given in the tenth dorsal interspace. Mayo operation, with resection of omentum and return of bowel. Respiratory and cardiac failure of about ten minutes' duration. Oxygen and artificial respiration, and adrenal blood-pressure-raising principle, 3 min., in saline solution intravenously. While there was no evidence of superficial circulation and the patient appeared as one dead, we were not positive as to absolute cardiac arrest. The patient revived, but died four days later of progressive peritonitis.

CASE VI.—*Respiratory and cardiac failure in a patient with strangulated hernia. Successful resuscitation. Complete recovery.*

T. M., aged 56. Asthenic. Strangulated inguinal hernia of about thirty hours' duration. At 3.40 P.M. the patient received $\frac{1}{100}$ gr. of scopolamine and $\frac{1}{6}$ gr. of morphine. At 7.15 P.M. he received $6\frac{1}{2}$ cg. of alcoholized amylene hydrochloride in the twelfth dorsal interspace. At 7.20 P.M. the operation was started, and it was finished fifteen minutes later. The patient vomited and there was failure of respiration and circulation. Artificial respiration was practised, and intravenous injection of salt solution containing 10 minims of epinephrinized solution given. The patient was revived in about ten minutes, but the circulation soon diminished in volume, so that at 8 P.M., when he was returned to his bed, no pulse could be detected and the temperature was 94°. The patient remained pulseless until 9.05 P.M., when it was possible to count his temporal pulse as 84. The later history was uneventful. The patient was discharged cured fifteen days after admission.

CASE VII.—*Respiratory and cardiac failure in a patient with large uterine fibroids. Artificial respiration for twenty minutes required. Operation completed. Recovery.*

Mrs. D., colored, aged 49. Multiple uterine fibroids weighing twelve and one-half pounds, which had first attracted attention four years previously. Respiratory cessation, with failure of circulation. Evidence of absolute cardiac arrest not obtained. Artificial respiration for twenty minutes. Eighteen ounces of saline solution with epinephrin given intravenously. Recovery.

CASE VIII.—*Respiratory and cardiac failure in a uremic and very septic patient. Successful resuscitation. Progressive uremia and death four days later.*

Miss W., aged 56. Uremia and sepsis from right pyelonephrosis and left nephritis. Patient very septic and in bad condition previous to operation. Operation under spinal anesthesia. Right nephrectomy and decapsulation of left kidney. Respiratory and cardiac failure. Saline solution intravenously, with 18 minims of epinephrin. Revived. Patient died four days later from sepsis and progressive uremia.

DISCUSSION.

Dr. Thomas E. Satterthwaite, of New York, said that it would be extremely important to know how long a patient apparently dead might survive under certain conditions, but that this was a subject of which little was known as yet. Dr. Babcock's experiences were therefore of great interest to the profession. Of the two forms of death, by failure of the circulation and of the respiration, sometimes the heart gave out first, sometimes the lungs. When an interne at the New York Hospital he had practised a method of artificial respiration which in his hands had often proved effective. The abdomen is compressed and the contents are pushed upward with the right hand, while at the same time the root of the tongue is depressed, and this organ drawn somewhat out of the mouth with the fingers of the left hand. The right hand presses upward rhythmically, at first a few times a minute, the movements gradually increasing in frequency. A towel, handkerchief, or something of the kind is put in the corner of the mouth, to protect the hand from the patient's teeth. This method had been published for a score of years in Wood's "Physician's Visiting List" and in 1885 was described

in Wood's "Reference Handbook." He had never found it necessary to introduce a tube into the trachea. Regarding the blood-raising principle of suprarenal gland, he was on record as having advised caution in the use of this drug. In one instance, while making some experiments at the Physiological Laboratory of Columbia University with the intravenous injection of 5 minims of a 1: 1000 solution of the chloride of the principle, he found that intense flushing of the face and violent headache were produced in the human subject on whom the injection was used. In fact, the man declined to have the injection repeated. Unpleasant symptoms continued until the next day. Dr. Satterthwaite felt that, while the action of this remedy was prompt, it was so extremely powerful that an intravenous injection of the strength mentioned might easily be dangerous. He thought it better to commence with a small dose and repeat it at suitable intervals. As contradistinguished from intravenous injections, the hypodermic or intramuscular injections would to some extent act as a stimulus, but these were uncertain in their action and should not be relied upon in emergencies.

Dr. P. S. Pittenger, of Philadelphia, at the request of Dr. F. E. Stewart, made some remarks in regard to the dosage of the active principle of suprarenal gland. His experience, he said, had been entirely with animals. He found that from 12 to 16 minims of a 1: 1000 solution will generally produce a maximum rise in blood-pressure when injected intravenously into dogs of medium weight (6 to 12 kilos). Of course, the rise produced varied considerably with the difference in susceptibility in the different animals injected. Generally, however, an intravenous injection of from 6 to 8 minims of the solution named would produce a rise in blood-pressure ranging from 30 to 70 mm. of mercury.

Dr. Babcock having replied to a question by *Dr. Oliver T. Osborne*, of New Haven, Conn., as to what anesthetic he employed in the last case reported in the paper, that he had used spinal anesthesia with para-aminobenzoyldiethylaminoethanol hydrochloride, Dr. Osborne said that he wished to register his emphatic protest against the use of large doses of morphine and scopolamine previous to anesthetization with ether or chloroform. Aside from the effect upon the blood-pressure and other conditions, by such a procedure one produced profound narcotic poisoning from two or more drugs. Another point: general anesthetics were given to stop shock, but spinal anesthesia did not have this effect. As to the proper dose of the epinephrin, the speaker agreed with Dr. Satterthwaite that 5 minims of the solution mentioned was a dangerous amount. He believed in the use of a solution of 1: 10,000, and very little of that. The reason why the solution of 1: 1000 given hypodermically did not do harm in some cases was that the patient did not get all of the dose into his circulation at once. Personally, he had been making a study of all the anesthetics now recommended or in use, and he had come to the conclusion that the thoroughly trained anesthetist could employ almost any anesthetic without injury to the patient. This was certainly not the case, however, with the unskilled administrator, and, as he had stated, he believed it to be especially dangerous to advise morphine or scopolamine as a preliminary to the anesthetization.

Dr. Spencer L. Dawes, of Albany, N. Y., said he wished to express his entire agreement with Drs. Satterthwaite and Osborne in regard to the danger of too large doses of the suprarenal principle. He would like also to record his protest against the use of such narcotics as morphine and scopolamine as a preliminary to general anesthesia, as well as the use of that particular class of anesthetics in the hands of any but the most experienced.

Dr. Charles E. de M. Sajous, of Philadelphia, said that many points had been brought up which instanced the prevailing lack of knowledge concerning the physiological action of these remedies. Before we administered an anesthetic we should fully understand the manner in which it causes the cellular elements of any tissue to modify their functional activity. Textbooks taught, for example, that morphine diminishes pain by causing the cerebral sensory centers no longer to take cognizance of the stimuli

received from the periphery. How did it accomplish this? Certainly, the answer was not afforded by the explanation just given, which in itself only described an effect, but not the *modus operandi* of that effect. Analysis aided by the microscope would show, however, that morphine caused constriction of the arterioles which supply the sensory centers of the brain to which the pain impulses arrive; receiving less arterial blood, their sensibility was necessarily reduced, and the pain impulses were not perceived. If we now bore in mind that morphine has a similar action upon the arterioles of the whole organism, it would become plain that in giving morphine as a preliminary to anesthetization we added an agent which might block the circulation into the tissue elements, and thus terminate life by arresting the functions of vital organs, such as the heart. There was need of a more careful physiological study of the causes of drug action. The laboratory worker was too often a mere registrar of experimental facts who exercised very little his reasoning faculties to ascertain the manner in which the phenomena recorded were produced.

Dr. A. Ernest Gallant, of New York, said the paper applied to surgical cases, and it seemed to him that the speakers in the discussion had treated of matters which were foreign to it. When a patient was to all intents and purposes dead, one was certainly justified in running some risks in the effort to bring him back to life again. The case was entirely different when we were treating patients who were in no such desperate straits. It was to be borne in mind that Dr. Babcock's cases were surgical ones and cases where death occurred upon the table, and that in such instances one ought to give a remedy freely enough to get the effect desired, and never mind the dose. In these cases of collapse the tongue did not fall back unless the head was permitted to fall back. Upon the operating table the head was generally placed too low. Now, if, when the respiration failed, the head were brought well forward, the tongue and the jaw could not fall back. As had been clearly demonstrated by Hare, the pharynx was widest open when the head was bent farthest forward. As to the difficulty of getting a soft-rubber tube into the trachea, it seemed to him, from the experiences of obstetricians with asphyxiated babies and his own experience in intubation for laryngeal diphtheria, that this had been exaggerated. If one ran his finger down to the base of the tongue and pulled the epiglottis open, it did not seem to him that the introduction of the tube would be a difficult matter.

Dr. Alfred C. Croftan, of Chicago, called attention to a method of resuscitation in anesthesia, stating that he first heard of it from a country doctor who was accustomed to doing "farmhouse surgery." This method was analogous to the treatment of asphyxiated babies by swinging. The method employed was to pick up the patient, have her hang over the shoulders of a strong farmhand, and swing her to and fro rhythmically. In the absence of the necessary emergency paraphernalia, this method seemed decidedly worthy of trial.

Dr. N. P. Barnes, of Washington, D. C., wished to refer to a method of artificial respiration mentioned by him in the *International Clinics* of 1905. A patient is brought to the edge of the table, face downward, and chest inclined to favor the expelling of water, mucus, or blood from the lungs. The abdominal muscles are fixed by the unyielding table, and the operator, kneeling or standing over the back of the patient, makes pressure downward upon the lower ribs, thus expelling the air. Relaxing the pressure on the ribs gives play to their convexity, thus drawing air into the lungs. These pressures and relaxations are continued rhythmically at intervals of five seconds, the individual being thus forced to breathe rhythmically without effort on the part of the patient or operator.

Dr. Babcock, in closing, said the danger from epinephrin, he thought, could be obviated if proper care were observed in its administration. His apparatus consisted of a 6-ounce glass funnel, six feet of rubber tubing, and a hollow needle. For use this simple apparatus was to be filled with salt solution and the needle properly introduced into a vein. There was then dropped into the funnelful of warm normal saline from 1

to 5 drops of 1: 1000 epinephrin solution, according to the urgency of the patient's condition. He then kept on adding more of this until he obtained a sufficient effect. Some of his cases had had as much as 15 or 20 minims of the solution. As soon as the cardiac effect was noted the tube was clamped or the injection of simple saline solution substituted. In this way the agent could be used intermittently for fifteen minutes to an hour, as was required. The employment of epinephrin subcutaneously was to be avoided, from the slight cardiac effect produced and from the great danger of local necrosis. During the efforts at resuscitation it was, of course, important that the patient's head be lowered. He was not convinced as to the advantage of Crile's arterial injection of epinephrin. In regard to the preliminary use of morphine or scopolamine in the production of anesthesia, he thought that the cases in which such drugs were to be employed should be selected with care. He certainly would exclude them from any patients with seriously damaged hearts or lungs, or with grave impairment of the nervous system. He desired it to be understood that the methods to which he had referred did not apply exclusively to surgical cases, as they could be employed in drowning and in other cases where resuscitation was called for, and also that he had employed the method in patients who had not had spinal anesthesia.

SOME COMMON TYPES OF HYPOSECRETION OF THE THYROID.

By OLIVER T. OSBORNE, M.A., M.D.,

Professor of Therapeutics, Yale Medical School,

NEW HAVEN, CONN.

It is the object of this paper to present a few types of what I consider hypothyroidism, or symptoms of subthyroid secretion. Many of these conditions are not recognized, and patients suffering from disturbed physiology of this gland drift from physician to physician, and are improved only after the diagnosis has been made and the proper treatment inaugurated. Unquestionably, many of these patients are psychopathic and may improve by mental treatment. The thyroid gland is peculiarly susceptible to mental stimulation and to mental depression, and anything that quiets mental excitation will diminish a hyperthyroid secretion of the gland, and anything that removes mental depression will increase a subnormal secretion of the gland.

Some instances of disturbed secretion of the thyroid, a few of which I shall relate, look like pure hysteria, or that disturbed nervous state which we call neurotic, but for the pathology of which we are still searching. Therefore, many will ascribe the favorable results obtained by treatment of the thyroid as simple instances of mental impression.

The physiological activities which a normal thyroid is expected to furnish may be summed up as follows: It is a necessary stimulant to growth in childhood, both bodily and mentally; it is always a stimulant to mental activity and to proper cerebration; it takes active part in the deposition and distribution of fat; it takes an unknown but important part in nitrogen metabolism, and many times it is an active opponent to nitrogen poisoning; without its activity proper genital development is impossible, and the secretion of the genital organs is imperfect. It takes an active part in the function of menstruation and in the development of the fetus in pregnancy. During the repeated periods of menstruation and during pregnancy it normally furnishes an extra amount of secretion. If it does not do so, the menstrual function is imperfect, the woman during pregnancy is abnormal, and parturition is likely to develop eclampsia and the child is likely to be born a cretin.

The thyroid gland, while present in the young infant, reaches its full development only at puberty, and after 45 begins slowly but progressively to furnish a diminished secretion; the gland gradually atrophies in old age. This atrophy or diminished secretion seems to allow an increased connective-tissue development in various parts of the body, notably in many organs; in other words, its atrophy allows sclerosis, and its early atrophy or early insufficiency causes early sclerosis.

The gland has a good deal to do with the condition of the blood. This, however, is not well understood. At times, too much of its secretion causes

hemorrhage. At other times, an insufficiency of its secretion allows or causes hemorrhage. This difference in action is perhaps due to the facts that too much secretion dilates the blood-vessels (the gland furnishes a secretion which is a vasodilator), which may allow or cause hemorrhages from mucous membranes, as from the nose or from the uterus, and that subsecretion must sometimes allow a condition of the blood to occur which is not dissimilar to that of hemophilia, or to that condition which occurs in patients with hemorrhagic diathesis; in other words, a very aplastic condition of the blood, perhaps a diminished calcium content. It seems, at times, to have something to do with stimulating or encouraging the production of red blood-corpuscles, as in the condition of chlorosis, if it is not properly functioning.

When it is considered how little secretion the thyroid furnishes per hour or per day, and that this secretion is picked up by the blood as it passes through the normal thyroid, it is not surprising, when there is an enlarged thyroid from normal hypertrophy, such as occurs in Graves's disease, and especially when the blood-vessels are dilated as seen in many such cases, that the blood, acquiring so much more thyroid secretion in a given time, must of necessity produce the intoxication that we see in this disease. An enlarged thyroid with large, dilated vessels has been estimated to allow the whole blood of the body to pass through the gland at least once an hour. When it is remembered that thyroid feeding may produce prostration and dangerous symptoms, it is easily understood why, in Graves's disease, the blood thus loaded with thyroid secretion causes such serious and sometimes dire symptoms.

As above stated, various mental conditions stimulate or depress the thyroid. This is true of some functions, foods, and drugs which act on the thyroid. The stimulants to thyroid secretion are great sorrow, great joy, and nervous tension; sexual excitement, genital disturbances, especially uterine, and pregnancy; cerebral stimulants, such as coffee, tea, and alcohol; and such drugs as arsenic, iodides, phosphorus, salicylic acid, pilocarpine, and, of course, thyroid extract. The idiosyncrasy of some patients to iodides I believe to be due to an extra susceptibility of the thyroid. Depressants to thyroid secretion are: quiet, seclusion, and absolute rest; absence of all sexual excitement and all genital irritation; a milk or milk and cereal diet; lime, perhaps in almost any form, but especially as the glycerophosphate; most hypnotics, especially bromides and chloral; opium as a quieter of all glandular activity, possibly by quieting the mental activity and stupefying it, and ergot.

I can only express once more my hope that the physiological chemists will soon be able to differentiate the various elements of activity of the thyroid gland. Histologically, the thyroid may be perfectly normal, and yet it may be furnishing a secretion that is disturbed, *i.e.*, the relation of the different elements to each other is abnormal, and yet, as a whole, the gland will be neither oversecreting nor undersecreting. Such a differentiation would explain the varying symptoms caused by subsecretion and would account for the fact that such symptoms are not improved when the whole gland is fed.

When the very active part that the thyroid gland takes in the life of the female is recognized, it is not to be wondered at that thyroid instability so

frequently occurs in women, and that the normal activity of the gland is so often increased at times when it should not be increased, or, on the other hand, that, having been so many times normally hypersecreting during the woman's life and so many times not returning quickly to normal when such hypersecretion is not needed, the gland becomes overworked and finally hypofunctionates. This thyroid instability, at times hypersecreting, at others hyposecreting, can account, as no other one etiological factor can, for the so-called neurotic women who have at one time an asthma, at another time an urticaria, then an eczema, then a diarrhea, then perhaps joint pains, then unexplainable vomiting, then headaches, then tachycardia; each condition when present urgently calls for treatment, while improvement is followed by another abnormal condition.

As I propose to offer a few clinical histories of patients who have hyposecretion of the thyroid, I will first present a list of the conditions for which I think subsecretion of the thyroid may be responsible. These are: cretinism, slow growth in children, some types of eczema, some forms of asthma, infantile obesity, chlorosis, amenorrhea, some digestive disturbances, some forms of epilepsy, some forms of gout, depressant hysteria, sometimes the vomiting of pregnancy, some forms of eclampsia, some forms of melancholia, adiposis dolorosa, lipomatosis, myxedema, senility, and perhaps Raynaud's disease.

The following case shows the improvement caused by the feeding of thyroid to a defective child:—

Case I.—*History.*—The patient, a girl, was first seen when she was 3 years old. She was the mother's first child, and, though not a cretin, was fat, rather large for her age, very backward about talking, and did not walk until she was 2½ years old. She had four teeth when she was 5 months old, and twenty when 18 months old. She was cross-eyed and pot-bellied, a large eater, and the bowels tended to be loose. She did not tell when she desired to urinate, and could not control the bladder. Adenoids had been removed, but the patient drooled a great deal, and could say but two or three words, and there had been no improvement in this line for three months. She was very nervous and did not sleep well; cried a great deal, and would not play by herself. There was no history of any sickness; she never had had any eruptions or a convulsion. The father and mother were both perfectly well. Physical examination was negative, except as above stated.

Treatment and Course.—The patient was given 1 grain of thyroid substance twice a day for some time, and then once a day for many months. In two months there was marked improvement; she slept well, cried less, and grew taller; the abdomen became normal and the disposition improved; she told when she desired to urinate and began to talk more. When first seen she walked inco-ordinately; this also improved, and in two months the patient fell but very infrequently. In about two years she began kindergarten work and continuously improved in all lines.

I had this child under observation for about three years. The mother of this child, aged about 30, became pregnant two years ago, and, lest she should give birth to another child who had subthyroid secretion, I gave her 3 grains of thyroid a day during the last three months of her pregnancy. She gave birth to a male child which weighed 14½ pounds and was fine and perfect in every way.

The types of eczema which are improved by thyroid treatment are those which occur in babyhood and childhood around the orifices of the body and as fissures in the skin. The dry, scaly eczemas and the itchings of old age are also benefited by thyroid. Patients with dry skin, with or without powdery desquamation, in all grades up to real ichthyosis, lasting often a lifetime, show improvement after thyroid. The following two cases show the value of thyroid in these conditions:—

Case II.—*History.*—The patient, a young unmarried woman aged 26, was first seen four years ago. Her skin, especially of the hands, abdomen, and legs, since childhood had always been rough, harsh, and almost like a mild ichthyosis. The epidermis peeled off in clouds and showers of dust every time she removed her clothing. She had never perspired normally, and was always very cold in winter.

Treatment and Course.—After a month or two of thyroid treatment the skin became softer; the patient said that the epidermic scaling was less than it had been since she could remember. The following winter she felt the cold less than she ever had. Her general health also improved. She was given thyroid on an average of 2.5 grains a day, sometimes more and sometimes less, for a year.

Case III.—The patient, a man aged 61, had had more or less general eczema for two years. He suffered terribly from burning sensations and from itching, and always felt the cold greatly. He had received all kinds of treatments. He was put on thyroid, and almost immediately there was less itching; the skin felt better and he did not feel the cold, and in a month there was great improvement. He was then not seen for several months, when the same symptoms were beginning to return. He was put on thyroid treatment and again improved.

Sometimes the etiological factor in asthma is, as all know, very difficult to determine. Without enumerating the many causes, suffice it to say that occasionally a disturbed thyroid secretion is the cause, and that the securing of an increase in the secretion of the thyroid cures the patient. The following is an example:—

Case IV.—*History.*—The patient, a married woman aged 42, had suffered from a cough, off and on, for eight years; for the last two months before I saw her she had had it steadily. She raised both mucus and pus, but never any blood. The menstruation was regular, but had been scanty for a year. She never had had any severe illness. She had had six children; the youngest was 3 years of age. The family history was negative. She was wheezing with a typical asthmatic condition, and had great dyspnea on the least exertion. She had had a bad asthma attack six months before, the first one she had ever had. She had lost twenty pounds within a short period. The present attack of asthma had lasted two weeks. The sputum was negative as to tubercle bacilli. The thyroid was small. The diagnosis was asthma due to impaired thyroid secretion.

Treatment and Course.—To activate the thyroid the patient was given 3 grains of sodium iodide three times a day; she began to improve immediately; the asthma and cough disappeared and she gained two pounds in four days. The iodide was then reduced to twice a day, and in another week she had gained six pounds, and was feeling well in every way. The iodide was then reduced to 3 grains once a day, and in a week she considered herself cured. The successful action of this small dose of iodide was as an activator of the thyroid gland.

The next case shows an interesting story of various subthyroid disturbances:—

Case V.—*History.*—The patient, an unmarried woman aged 40, came to me complaining of abdominal distention, which she had had for three years, and which had

become worse during the last six months. All kinds of diagnoses had been made of various intestinal indigestions, disturbed circulation, etc., for which she had been treated. The bowels moved three times a day; this had been a habit for years, and she did not call it a diarrhea. Menstruation was regular. She had some palpitation and some little dyspnea, and at times she thought she had an asthma; she could not sleep well at night on account of it. She had had a slight cough for a good many years, frequently raising mucopus; she was subject to hay fever and asthma in the summer. She felt weak all the time, and said that her feet and legs occasionally swelled at night. She had lost weight. The pulse was slow, down to 54. The lungs were asthmatic; heart normal; abdomen negative, except that it was tympanitic. The urine was negative. Diagnosis, hyposecretion of the thyroid.

Treatment and Course.—The principal treatment was thyroid, at first 5 grains a day, then 2½ grains a day, then 2½ grains every other day; ten days from the time she started the treatment the patient stated that she had not been as well in every respect for three years.

The following case is interesting as showing a combination of asthma and eczema:—

Case VI.—*History.*—The patient, a girl aged 6, was subject to recurrent colds, with asthma. She had somewhat enlarged tonsils, was pale, a poor eater, and had a more or less constant peculiar skin eruption; it was not eczema and not itch, although the first appearance looked like scabies. The child never perspired. The diagnosis was insufficient thyroid secretion.

Treatment and Course.—The patient was given 1 grain of thyroid a day for some weeks. Very soon the eruption and asthma disappeared and the child improved and became well. I did not see her again for one and one-half years, when she again had an asthma. At this time I gave her 3 grains of sodium iodide three times a day to activate the thyroid gland. She did not improve. The asthma was no better. I gave her 1.5 grains of thyroid once a day, and the asthma quickly disappeared. I did not see her again for two more years, when she had the same recurrence of asthma. Thinking that she was old enough now for the iodide to stimulate the thyroid, I gave her 3 grains of iodide three times a day. This acted as I expected, and the asthma quickly disappeared.

Amenorrhea is very successfully treated with thyroid; chlorosis will often improve as rapidly with thyroid as with iron or arsenic. In fact, I know of no emmenagogue which acts as well as thyroid. Whether in large doses it could cause abortion I do not know, but certainly in delayed menstruation in young girls and in amenorrhea at almost any age, especially if there are other symptoms of insufficient thyroid secretion, as putting on of weight or drying of the skin, thyroid is almost a specific.

It is rarely recognized that a number of digestive disturbances can be due to insufficient thyroid secretion. It is recognized, however, that hypersecretion of the thyroid can cause such disturbances. These disturbances are mostly diarrheas. The exact reason that insufficient thyroid secretion causes indigestion, and especially intestinal indigestion, is at present difficult to understand. The following is a very interesting instance of the successful use of thyroid:—

Case VII.—*History.*—The patient, a boy aged 8, was brought to me two years ago with the history that three and one-half years before he had had an acute intestinal attack of some kind with which he was seriously ill for months. Since that time, off and on, at intervals, he had had these intestinal upsets, with bad diarrhea, and at this time frequent involuntary movements. He also at these times had albuminuria. There was

a peculiar pigmentation on the hands and neck and a little on the face; also there were some leucodermic spots on different parts of the body, especially the neck and hands. He had also some of this dark pigmentation on his thighs and lower abdomen. All sorts of diagnoses had been made and all sorts of treatments had been instituted, all more or less unsuccessfully, although sometimes these diarrheal attacks seemed to become better under some treatment, only to recur again. The heart, lungs, abdomen, and urine were negative. A few of the cervical glands were palpable.

Treatment and Course.—The patient was given thyroid, and electric treatment to the imperfect anal sphincter. The sphincter soon became competent, and the boy improved in every way; the diarrheal attacks entirely disappeared, and after having been for years on a rigid diet he was now allowed all kinds of assorted food. The pigmentations and leucodermic spots gradually disappeared, and the patient became well. The thyroid treatment in small doses was continued for some months and then stopped, and in April, 1911, a year after I had first seen him, the patient began to have a little trouble again in the way of diarrhea, followed by constipation; also there were some abdominal pains, and puffing and swelling in different parts of the body, especially under the eyes. He had little irregular temperature attacks; sometimes palpitation of the heart. He was again given thyroid, again he improved, and the pigmentations, which had more or less returned again, faded. The boy, with slight disturbances, is constantly improving, growing, and doing finely. The last time I saw him was in December, 1911.

If epileptic attacks occur at the menstrual periods, or at regular four- or five- week intervals during amenorrhea, or develop at the menopause, disturbance of the thyroid is often the active or exciting cause, and the disturbance is generally a subsecretion. The reason that thyroid has been used unsuccessfully so many times in epilepsy is that the cases have not been properly selected. When thyroid is properly administered in the above-described class of cases, many times improvement and sometimes absolute cures take place, and any treatment that is successful without the use of enormous doses of bromides is certainly good treatment. The following is a case of great interest to me:—

Case VIII.—*History.*—The patient, a girl aged 17, first came to me in April, 1904, with the history that from July, 1903, she had had peculiar sleeping attacks in which she would be almost in a comatose condition for two or three days. These attacks kept increasing in frequency, averaging at first once a month and now twice a month. In the last attack or two she had shown some stiffening, but had never had any convulsive movements, although she had made slight noises and had a little frothy mucus appear at the mouth. In the last attack she slept but twelve hours. After these sleeping attacks she could not hear for several days, and could not see well for two or three days, at times being almost blind; she did not recognize her family for several days. She lost her voice for nearly a week, and during these days did not recognize her own clothing, jewelry, etc. In some of these sleeping periods she did not appear even to breathe; she took no nourisment and no liquid, and at times passed no urine for from two to three days. Menstruation began when the patient was 14 and was slightly irregular, generally occurred every five weeks, and lasted four or five days. The sleeping attacks had generally occurred just before the period. Physical examination was negative in every respect, except that there was a slightly movable right kidney, and the thyroid gland seemed enlarged, though evidently subsecreting. A diagnosis of epilepsy and catalepsy was made, and the fact that these attacks occurred just before the menstrual period and were worse if the period was delayed, gave the indication for treatment, viz., to hurry menstruation and to antagonize whatever toxins might be in the blood at that time. Thyroid is an antitoxin, probably, of protein poisons.

Treatment and Course.—The patient was given thyroid from April, 1904, and she never had another one of the sleeping attacks. In June she had a typical slight epileptic attack. In January, 1905, she was still doing finely, but had had two attacks of losing herself for from two to ten minutes after slight injuries; in other words, *petit mal* attacks. In May, 1905, having stopped the thyroid for some months, she again had several epileptic attacks in one day, followed by a prolonged sleep. Thyroid again stopped this. She married in August, 1905, and was not seen from that time until November, 1910, during which time she had had no recurrence of fits or sleeping attacks, but she now complained of hot flashes, fainting periods, and some irregular swellings. She was again given thyroid, with small doses of iodide, and I have not seen her since, but I feel sure that she would have come to me had there been any recurrence of the trouble.

Case IX.—Five years ago the mother of this patient, aged at that time 44, had an attack of what was called rheumatism, and was sick for a number of weeks in a New York hospital. The rheumatism was located in the legs, and there were peculiar hemorrhagic spots all over both legs. She also, while in the hospital, had recurrent bleedings from the kidneys. She had been given the usual treatments, but, receiving no relief, she came to me, hardly able to travel. Knowing the history of the daughter and the tendency of thyroid disturbances to run in families, I decided to give her thyroid. The bleeding ceased within two days, and the petechiæ rapidly disappeared, as well as the rheumatic symptoms, and a number of years after there had been no recurrence.

The exact relation of thyroid secretion to the normal plastic condition of the blood is not known. Ordinarily, feeding thyroid will stimulate bleeding possibly by causing a dilatation of the blood-vessels, particularly of the uterus and nose, but instances not infrequently occur when the feeding of thyroid in hemophilia stops the bleeding. An interesting instance of its action was in an overweight woman at the menopause who, in spite of all the ordinary treatments, including calcium, epinephrin, ergot, atropine, digitalis, etc., bled profusely from the nose, gums, ears, stomach, intestines, and bladder; the urine passed seemed almost pure blood. The woman was nearly exsanguinated. This was four or five years ago, and rabbit- or horse- serum injections were not tried. From the history of having put on a good deal of weight and of sleepiness, I advised the administration of thyroid. The patient was given large doses of thyroid, and in twenty-four hours the bleeding ceased and did not recur until a week later, when, the thyroid having been stopped for two days, there was a slight recurrence. On the readministration of the thyroid, the bleeding again ceased.

Subsecretion of the thyroid can cause mental depression to all intensities, from simple apathy and indifference through depressant hysteria to actual melancholia. Administration of thyroid to such patients always causes improvement. Activation of the thyroid with small doses of an iodide in cases of mild subsecretion of the thyroid causes cerebral stimulation and satisfactory improvement. The obverse of this is well known, viz., that the administration of either thyroid or an iodide in Graves's disease will always increase the disturbance.

The most frequent of all hypothyroidism instances are those associated with added weight. These symptoms grade from the simple putting on of flesh after 40, especially in women after the menopause, to adiposis dolorosa, lipomatosis, and myxedema. The symptoms of typical hypothyroidism are scanty or absent menstruation, fat deposits on the breasts, upper arms, at the clavicles, hips,

and upper part of the thighs, and, at times, the abdominal apron, which may hang over the pubis. Other associated symptoms are drowsiness, slow pulse, dry skin, puffiness of parts of the body at various times, and, perhaps, slow mentality. Instances of this type of patient are so frequent that it is hardly necessary to present clinical histories. Other symptoms of subthyroid secretion are puffing under the eyes and of the hands and feet, without kidney or cardiac lesion. This puffiness is not a real edema and may occur asymmetrically or symmetrically and at irregular times of the day; it is often worse in the morning. The skin is likely to be dry in these cases. Sometimes a glycosuria is due to insufficient thyroid secretion, as it may also occur in hypersecretion.

The following case is unique:—

Case X.—*History.*—The patient, a young girl aged 16, was seen by me in consultation in 1905. The family history was negative. The patient had had convulsions when she was teething; was backward in school; began to menstruate when she was 14, but had not menstruated during the last year. She had attacks of fever, which had begun about a year before at the time the menstruation ceased. They lasted about nine days, to recur again in about three weeks. At the onset she had chills, headache, loss of appetite, pain in the abdomen, loose bowels, and insomnia. She had been treated for typhoid fever, for intestinal tuberculosis, malarial fever, and hysteria. During these fever attacks the temperature went above 103°, the pulse sometimes up to 130, and the respirations up to about 30. A diagnosis had also been made, on account of enlarged glands in the neck and enlarged spleen, of Hodgkin's disease, and the patient had been given repeatedly long-continued doses of Fowler's solution.

Examination.—It was during one of her fever attacks that I saw her. The glands of both sides of the neck, and also in the axillæ and groins, were somewhat enlarged; the pupils reacted slowly; the conjunctival reflexes were present; the heart and lungs were negative; the spleen was enlarged almost to the umbilical line and tender on palpation; the liver was apparently normal in size; the ovaries were not tender; the knee-jerks were exaggerated. The urine and the blood were negative. Just preceding one of those attacks of fever the mother said that the girl was listless, but still restless, and she (the mother) would know that a fever attack was about to begin. With this history and the repeated improvements and the continued recurrences it was impossible to make a definite diagnosis. On the other hand, the very fact of the periodicity and of occurrence about the time of the expected periods and that there was amenorrhea suggested the possibility that if the patient menstruated regularly she would not have these attacks of what was apparently a toxemia.

Treatment and Course.—The patient was given 5 grains of thyroid twice a day. In ten days she began to menstruate and was feeling well. The next month she menstruated again. Under thyroid medication, given intermittently, she menstruated every month until April, 1906, when she ceased to menstruate. Then in May, when I saw her again in consultation, she again had a temperature of 102°; abdomen was tense; spleen was enlarged; glands of the neck tender. She was given thyroid, and in a few days began to improve. In a few days the spleen and the glands were less tender and smaller, the temperature disappeared, and she became apparently well, and menstruated normally in June. This was in 1906. Her physician tells me that she was well until July, 1907, when, following a tonsillitis, the spleen again became enlarged and she had slight recurrence of the above symptoms. She was given thyroid, and in two or three days was again normal. She was well when last heard from in March, 1911.

Lest I seem to advise the frequent and careless use of thyroid, please let me urge that, when it is needed, but small doses be used, as it is potent for harm. When given to patients who should not receive it, it will make their

symptoms worse, and sometimes but a little of it will push a wavering thyroid gland to hypersecretion and Graves's disease.

It should be added to the list of poisons, and the laity should not be able to obtain it without a physician's prescription. Though much of the thyroid substance on the market is not active, a little coincidently administered iodine, as an iodide, will render it active.

DISCUSSION.

Dr. Charles E. de M. Sajous, of Philadelphia, said he was quite in accord with the views expressed in the paper. Had Dr. Osborne or himself ventured to express such views before a society such as this twenty years ago, hanging would have been considered almost too good for the culprit. The profound effect of the thyroid upon the vital process, and the phenomena observed when its normal secretion was disturbed, had been well set forth by Dr. Osborne; the variety of affections with which this secretion had to do was almost infinite, in view of the fact that it influenced profoundly cellular metabolism, particularly the catabolic phase of the process, the hydrolysis of waste products, and the immunizing power of the blood.

Dr. F. M. Pottenger, of Los Angeles, Cal., said that Dr. Sajous must indeed feel proud to know that his long and arduous labors were at last appreciated. When the first volume of "Internal Secretions" appeared he had had the pleasure of reviewing it for the *Southern California Practitioner*, and in the article he had said that changes in medicine were now being made so rapidly that we ought to wait before condemning any novel views, especially when, as in the present instance, they pointed to the development of a great field. In the preface to the second volume Dr. Sajous had expressed some measure of disappointment that his work had not been better received; but now we all fully realized that this work had come to stay. He cited one case which illustrated especially well the value of recognizing the existence of abnormal thyroid secretion. This was that of a young married woman whose condition was similar to that of one of Dr. Osborne's cases. She was suffering from pulmonary tuberculosis, but, aside from having the usual symptoms, was sleepy, listless, sluggish, and forgetful of her children and her household duties, and had in fact become a burden upon her family. In his study of her case he came to consider thyroid hyposecretion as the probable cause of her unfortunate condition. He gave her thyroid, and the result was that, in the language of her family, she was "made over." Without the work of Dr. Sajous and his followers, he felt sure that it would have been impossible to do anything for this patient.

Dr. Alfred C. Croftan, of Chicago, said that a clinical experiment seemed to substantiate the laboratory evidence of a disintoxicating effect of the thyroid secretion. There were cases of asthma attributable to egg-albumin intoxication. In two children that Dr. Croftan had observed an attack of asthma could promptly be inaugurated when even small quantities of egg albumin were ingested. In one of these cases egg albumin had been recovered in the urine by means of a specific precipitin reaction, showing that native egg albumin unconverted entered the circulation. The interesting point in Dr. Osborne's paper was that the administration of small doses of thyroid together with egg albumin inhibited the asthmatic attacks, showing with some degree of conclusiveness that the toxic effects of this foreign albumin are neutralized by the administration of thyroid. Dr. Croftan said that he welcomed this opportunity of congratulating Dr. Sajous for at last coming into his own, as far as the recognition of his pioneer efforts in the field of internal secretions was concerned. He expressed the hope that Dr. Sajous would keep and collect all the stones that had been thrown at him during the last ten years until he should have accumulated enough material to build himself a permanent monument.

Dr. R. D. Rudolf, of Toronto, inquired what the indications were for the administration of thyroid. There appeared to be a great variety of conditions, he said, which were dependent upon insufficient or otherwise abnormal secretion by the gland, and in which its use was attended with benefit; but how were we to decide when it was advisable to give it as a remedy? Again, as to the dosage—what amounts were to be employed? Beebe had called attention to the very different susceptibility of different individuals to the action of thyroid. How were we to deal with this inequality? It was a fact that, while the internal secretions had been placed upon a scientific basis by Sajous and others, the faith in their therapeutic value was founded on the most ancient beliefs.

Dr. Spencer L. Dawes, of Albany, N. Y., said that we should have definite views as to when thyroid was to be administered, how much was to be given, and what particular form was to be used—whether the thyroid extract, the serum, or the dried, desiccated thyroid. Indiscriminately used, it might be productive of much harm.

Dr. Osborne, in closing, said that he felt some diffidence in speaking on this subject because of the presence of Dr. Sajous, who knew so much more about it than he did. Personally, he never wrote out a prescription for thyroid unless he chanced to be giving it in association with other remedies, but made it a rule to dispense it himself. He therefore tried to get the best material available, and always kept on hand in his office specimens of thyroid from several of the most reliable producers. From disordered thyroid secretion there resulted all grades of conditions, ranging from those due to marked hyposecretion to those due to extreme hypersecretion. Included among these grades were borderline cases, in which one could not be certain at first whether the patient was suffering from subthyroid secretion or the reverse. In instances of this kind one might give a little iodine, when the ameliorating or aggravating effect produced would enable one to judge of the condition present. If benefit resulted, one might start in with 3 grains of thyroid in the form of good tablets; possibly also with 3 grains of sodium iodide. After about a week one would be able to tell whether it was advisable to increase the dose or not, and later the amount given could gradually be diminished.

NOTES ON THE DIFFERENTIATION OF CARDIAC ARRHYTHMIAS AND THEIR TREATMENT, WITH A NEW TIME-MARKER.*

By THOMAS E. SATTERTHWAITE, M.D.,

NEW YORK, N. Y.

The subject of cardiac arrhythmias took on a new phase as soon as graphic methods were used for their differentiation. Indeed, the use of graphic instruments has revolutionized the matter by disclosing new data of great practical value. Most of these discoveries have been the work of the last ten years. As a single illustration of the lines of investigation and their clinical results, it may be mentioned that Friberger[1] recently undertook to examine the hearts of 321 unselected children between the ages of 5 and 14, taking graphic records of each child. Only about 37 per cent. had regular pulses. Of the remainder about 12 per cent. had great irregularity and about 50 per cent. a moderate amount. The variety of irregularity was that which Mackenzie has called "the youthful type," and was about equally common in the two sexes. The etiology was not clearly evident, but Friberger found that in advanced tuberculosis there was arrhythmia in about half of those examined. This is only one of the many fields in which graphic methods are helping the practising physician.

It has now been generally accepted that arrhythmias may be satisfactorily classified with reference to the five physiological attributes of heart muscle, demonstrated by Gaskell in 1882. These are, as is now well known: (1) Rhythmicity, *i.e.*, the faculty of rhythmically initiating a stimulus. (2) Irritability or excitability, *i.e.*, the capacity for receiving a stimulus. (3) Contractility, *i.e.*, the faculty of responding to a stimulus. (4) Conductivity, *i.e.*, the ability to convey a stimulus. (5) Tonicity, *i.e.*, the power to maintain cardiac tone.

Four distinct varieties of arrhythmias corresponding to the first four faculties or attributes can be demonstrated by graphic tracings.

To the first of the forms to be described I have given the name *pneumogastric arrhythmia*, because of its close relation to pneumogastric influences. It was described by Kussmaul years ago, and has been called vagus, fundamental, sinus, normal, or respiratory arrhythmia. The word sinus implies that it is a variety of the rhythm that originates in the sinus venosus, *i.e.*, it is the normal rhythm. This pneumogastric arrhythmia is a variation from the standard cycle within physiological bounds. Though the cardiac cycle varies in length, the systolic phase is little altered comparatively, while the diastolic is considerably lengthened, and this latter feature is the chief characteristic.

[1] Upsala Läck. Förhandl., Jour. Amer. Med. Assoc., March 16, 1912.

It may be seen in a tracing of the radial pulse immediately after the apneic period of the Cheyne-Stokes respiration of uremia. Kussmaul called it the *pulsus paradoxus*. It is the pulse following a deep inspiration; hence the term "respiratory." It can also be caused by the act of swallowing, which is largely regulated by the vagus or pneumogastric; hence the term pneumogastric arrhythmia. Apart from graphic tracings, this form of arrhythmia is recognized by the finger on the pulse. It can usually be inhibited by a single dose of atropine, $\frac{1}{60}$ grain.

It is not well to attribute too much importance to an arrhythmia which is usually quite transient, functional in character, coming and going from slight causes. But exceptionally it may be of a more serious nature, as in tuberculosis, or after infective diseases, especially the eruptive fevers of children. It occurs sometimes in neurasthenia; also in overdosing by digitalis and probably other drugs which affect the cardiovascular mechanism. From whatever cause, it is a loss of the normal rhythm, the stimulus to which we believe originates, as I have said, in the sinus venosus.

In *extrasystolic arrhythmia* there are extra—that is, as it were, supernumerary—contractions, from stimuli that do not originate in the sinus, though in the main the regular or sinus rhythm is maintained. They are of two principal types: the *ventricular,* where the contraction originates in the ventricle, and the *auricular,* where it originates in the auricle. Take an example of what appears to happen in these cases. If for any cause the left ventricle fails to empty itself, the residual blood, acting as a stimulus, can make the ventricle put in an extra beat before the normal auricular stimulus has passed down to it. On the other hand, in dilatation of the auricle, as, for example, in advanced mitral stenosis, the incomplete expulsion of the blood into the ventricle may operate to produce a supplementary contraction, which would then be an auricular extrasystole. Strain of auricle or ventricle also might, and probably does, produce extrasystoles. These have been called "dwarf" systoles, from their small size; "premature" systoles, because the contraction is in advance of the normal period for the contraction, and "interpolated" systoles, because they are actually interposed between beats that are of the prevailing type at the time.

All extrasystoles are followed by a pulse period that is rather longer than the normal. In the ventricular form the length of the preceding pulse period added to that of the following pulse period is equal to the length of two normal pulse periods. In the auricular form the pulse period following the extrasystole is shorter than the corresponding compensatory pause in the ventricular form. Such systoles occur at regular or irregular intervals. They are illustrations of an abnormal irritability or excitability of the heart, and are most common in persons of a neurotic constitution. Sometimes these extrasystoles cannot be detected by the finger, but they are usually recognized upon auscultation, when the regular sequence of beats is occasionally interrupted by one or two short sounds followed by a brief pause.

When, in a radiogram (radial pulse tracing), it is noted that the length of the pulse period preceding the extrasystole, together with the pulse period

following, constitutes a length of two ordinary pulse periods, this is taken to mean that the extrasystole is ventricular, and, according to Mackenzie, that the stimulus originated in the His bundle, on the distal side of the node. But the points of origin of the stimuli may be in other parts of the tissue intermediate between auricle and ventricle. These matters are still engaging the attention of physiologists, and have not been absolutely determined.

In the auricular extrasystole the stimulation is thought to arise in the primitive tissue of the auricle. These extrasystoles can be seen in jugular tracings. A characteristic of this auricular extrasystole is that in the arteriogram the compensatory pause following is shorter than in the ventricular extrasystole, as already stated.

Extrasystoles occur under the most varying conditions. Coffee, tea, tobacco, and gastrointestinal distention are examples of determining causes; under these circumstances their occurrence may not be of very serious importance, though when they happen in toxemia, in convalescence, or in the weak heart their presence adds to the gravity of the situation. They may occur in conjunction with other cardiac manifestations, when they constitute a further complication.

Not infrequently the extrasystole is appreciable by the patient, who may feel a sudden thud in the precordium, perhaps with a sense of faintness. It may even seem as if the heart were going to stop; and, as a matter of fact, it may actually do so. I have had such a case, where the heart did stop for several seconds—how many I do not know. It may be remembered that a man named Nordini, an Austrian Pole, is said to have the power of stopping his heart for twenty seconds, and his statement has not, I think, been contradicted. But the extrasystoles are not always appreciable subjectively. To make them distinct, the patient should be told to run round the room a few times and then hold his breath. The extrasystoles are intensified by hurried movements.

The really most important function of heart muscle is contractility. A striking example of its abnormal characteristics is seen in the *alternating pulse*, which consists of an alternation of large and small beats. The alternation is continuous,—which distinguishes this type of pulse from extrasystolic arrhythmias. It may always be recognized and differentiated by graphic methods when other physical methods leave doubt as to the diagnosis. It is, however, a rarity.

Another example of abnormal contractility is seen in *auricular fibrillation*, formerly called *nodal rhythm* by Mackenzie, and one cause of the *permanently irregular pulse* of Hering. Here the cardiac cycles vary so much that there is no sequence of beats having the same length. This special characteristic was well shown in one of my cases of heart-block. The source of the difficulty is put at the auriculoventricular node, which governs auricular and ventricular contractions through the bundle of His.

In 1905 Cushny and Edmunds suggested that in some of these patients the cause might be auricular fibrillation, a condition in which component parts of the muscle wall of the auricle contract independently of one another,

and in such a disorderly fashion that it might almost be said auricular contraction as a whole was at a standstill. But it was not until 1909 that researches by Lewis on the lower animals showed, by comparison of the arterial and venous pulse tracings and electrocardiograms, that this so-called nodal rhythm, or permanently irregular pulse, was to be attributed to auricular fibrillation.

In fibrillation there seems to arise in the auricle a continuous shower of stimuli which, falling on the node, excite it to send stimuli to the ventricle as rapidly as the bundle (and so the ventricle) is capable of taking them up. At first the ventricular contraction is apt to be very rapid, and the patient may die rapidly of heart-failure. But if the ventricle can be made to beat more slowly, the patient may lead a useful and even vigorous life for some years. It is therefore very important to diminish the rate, and this is done in a remarkable manner by digitalis. The gravest sign is an increase in rate; say, from 100 to 150. The digitalis should then be pushed until there is a fall to 80. My experience tallies with Lewis's view; for in the permanently irregular pulse, relief only comes from the continuous use of digitalis or strophanthus. Hering recognizes this fact. Mackenzie believes, however, that a good deal can be done for the patient. He finds, for example, that the irregularity is most often associated with rheumatic hearts, usually those of mitral stenosis, and with the fibroid heart of senility. In fact, as the deposit of fibroid tissue is common in both these varieties of cardiac disease, it seems possible that the fibroid deposit is the cause. In one case of mine there was a fibroid tumor of the uterus, but its removal did not improve the cardiac difficulty.

According to Lewis, auricular fibrillation constitutes at least 50 per cent. of all irregularities, the disturbance of cardiac rhythm having its origin in the auricle, and being due to temporary or permanent inco-ordination of the musculature of this chamber. In a study of 106 cases he has reached the following conclusions, which differ somewhat from those of Mackenzie: The rate of the pulse may be reduced as low as 30, or increased as high as 200, but this in itself has little significance, because many beats of the heart may not reach the radial artery. The high rates, however, between 110 and 150, are the most common, and with these the irregularity is greatest. According to Lewis, the diagnosis rests on these points: 1. The absence of the normal auricular contraction, as seen by the absence of the wave in the tracing. 2. The presence of a ventricular beat having its origin in an impulse received from the auricle. 3. Special oscillations in the curve, which have been shown to be due to the continual contraction of the various parts of the auricle quite without system or co-ordination. 4. Constancy of this picture from patient to patient in respect to the three first points.

Fibrillation is responsible for most of the disturbances of the ventricular system. Indeed, in the vast majority of instances a sphygmogram showing that no two successive heart beats are of the same length implies the diagnosis of auricular fibrillation. To Cushny, Mackenzie, Wenckebach, Rothberger, Winterberg, and Lewis the credit of the discovery is due. Janowski has

known such a case to last five and a half years, Mackenzie ten years, I eleven and a half years.

Of the existence of auricular fibrillation there seems to be no doubt, but we are still lacking in an agreement as to the criteria necessary for its detection.

In affections of conductivity the normal stimulus, which starts in the sinus venosus, passes from the primitive tissue of the auricle over the bridge of His to the ventricle, may be delayed in its course, may not cross at all, or may be arrested beyond the bridge. Any one of these several conditions will produce *heart-block*, a term invented by Gaskell in 1882 to indicate arrest or blocking of the impulse normally conducted from auricle to ventricle.

The *pulsus infrequens*, improperly called the slow pulse, is rather certain to indicate a loss of conductivity. When, as happens in such cases, a pulse is found where only about 26 to 40 beats can be recognized at the wrist, an inspection of the jugular will usually show that the auricular contractions are really twice or even more times as frequent. This inspection should always be made, when, if the head is turned to the left, the beating of the vein can be seen in a good light, and the diagnosis made without the aid of graphic methods.

In health the a-c intervals show in tracings the time occupied by the passage of the blood from the auricle to the carotid, which is usually one-fifth of a second, though it may be two-fifths, and persist at that rate for years. In complete heart-block the a-c interval varies so much that the auricle may be said to beat quite independently of the ventricle. Where there is complete heart-block, the a-c intervals may be seen to vary so that no two have the same length. Manges[2] has recently given the history of a patient with incomplete and subsequently complete heart-block, in whom the auricular rate, as shown by graphic tracings, was 280 to the minute, the ventricular ranging from 40 to 70, which rate, however, was raised to 120 on two occasions by the use of atropine.

Among the most frequent causes of loss of conductivity are syphilis, fibrosis, and neoplasms. Since the cause of auricular fibrillation is the same as that of heart-block, though usually in the substance of the ventricle, the one may pass over into the other. The condition may also be due, and in several of my cases has been, to hemorrhage at the base of the brain, when pressure is brought to bear on the nucleus of the pneumogastric. Stimulation of the peripheral branches of the pneumogastric may also produce heart-block; likewise, aconitine, epinephrin, muscarine, physostigmine, and asphyxia. In a case of acute heart-block, recently reported to me by Waitzfelder, of New York City, the condition was evidently due to overdosing by digitalis.

According to Mackenzie, the stimulus may go through and the pulse be as high as 70, and then fail to go through, leaving the pulse at 30. Such cases should encourage us to use appropriate remedies to restore the heart's action. Certainly if there is the slightest suspicion of advanced syphilis, antisyphilitic remedies should be pushed to the limit.

[2] Medical Record, April 8, 1911.

It is important to know that a diagnosis in heart-block can be made without the use of graphic methods. At present we recognize four forms of this disturbed conductivity:—

1. *Acute* heart-block, due usually to the misuse of drugs.

2. *Partial* heart-block, where the stimulus is occasionally carried through, as shown by an alternation between the normal rate and the slow rate.

3. *Complete* heart-block, where the auricle and ventricle contract independently.

4. The *Adams-Stokes syndrome*, where loss of conductivity is associated with syncopal attacks. The syncopal attacks are often attributed to cerebral anemia, induced by the slow action or temporary suspension of ventricular systole.

As for Gaskell's fifth attribute of cardiac muscle tonicity, it may be said that the loss of it is exemplified in the dilated heart.

Treatment.—In the matter of treatment, in (1) disturbed rhythmicity, the first type of irregularity discussed, it is quite evident that, as a rule, this condition does not justify our sounding notes of alarm. In other words, it is physiological, as, for example, in the so-called youthful type of irregularity. Consequently no treatment is required.

In (2) extrasystole there may be a neurotic basis, or the condition may result from the pressure of gas produced by gastrointestinal fermentation. Again, it may be a reflex from the gastrointestinal tract, as in indicanuria. In the one case, sedatives, such as camphor or the bromides, are useful; in the latter, remedies that regulate gastric or intestinal digestion, such as pepsin, pancreatin, bismuth, sodium bicarbonate, etc. If the extrasystoles are due to the excessive use of coffee, tea, or tobacco, the therapeutic indications are evident.

In (3) auricular fibrillation there is no remedy so satisfactory as digitalis or its congeners, of which strophanthus is next best. Only the most reliable active principles of these drugs should be used, because if given in suitable doses they are effective without causing any of the unpleasant effects usually associated with these drugs in other forms. The intelligent use of baths and resistance exercises is also very valuable.

In (4) heart-block, if it be acute and caused by digitalis, the use of the drug should, of course, be suspended at once. If syphilis exists, antisyphilitic remedies should be used according to our established rules, and in sufficient quantities. Atropine, $\frac{1}{60}$ grain, is available as a test to determine whether the heart-block is due to a lesion of the pneumogastric; it will usually increase the rapidity of the ventricular contractions, when these are below the normal, but it exerts no curative effects.

It is evident that graphic methods are useful not only in diagnosis with reference to treatment, but also as a register of actual facts. Certainly no large medical institution should be without a good polygraph.

A New Electric Time-marker.

Owing to the length of time required to procure a Jacquet time-marker, its initial expense, duties, and express charges, I have undertaken to devise an American time-marker, which can be made at home and involves no great expense. The instrument is actuated by two ordinary dry-cell batteries. These are connected by wires with the two more distant binding posts of a switchboard, the current actuating the platinum interrupter of a clock. The current passes ultimately to the signal magnet and vibrator. The pen-arm or lever of this magnet vibrates as often as 100 times per second. Fine adjustment screws regulate the excursions of the pen-arm. The kymograph used is the one known as the slow and fast combination model of the Harvard Apparatus Company.

DIGITALIS THERAPY.

By HENRY BEATES, Jr., M.D.,

PHILADELPHIA, PA.

Whereas discussion relating to digitalis therapy has been and is commonly limited to that narrower field of its usefulness, the cardiac lesions, your attention will here be directed to a consideration of the value of this drug in that larger and important group of disorders, the nutritional diseases. These have to do with the life and functions of *the cell,* and, therefore, involve problems of the assimilation of pabulum, the conversion of food principles into energy, and what, in a broad sense, is included in the processes of metabolism and function. Pabulum is necessary for the maintenance of cell life, and also for the supply, *to the cell,* of those substances which are to be functionated. The phenomena of kinetic and potential energy and certain problems of physical chemistry and biochemistry have, therefore, to be briefly reviewed in order to refresh our minds with the involved fundamental principles.

Time will be saved and the several associated laws demonstrated by the following quotation from the work of Leonard Hill entitled, "Recent Advances in Physiology and Biochemistry": "Experiments on any form of energy consist in observing the interactions between it and other forms; in studying the nature of the transformer, and of the changes, if any, which occur in it. The structure of the cell must, hence, be taken up from the point of view of its functions, and we must study its chemical and physical composition, the effect of the constituents upon one another, and upon the medium in which the cell lives." To this point, the medium in which the cell lives, attention is especially directed, because those phenomena of the living cell with which the clinician is therapeutically related, in the treatment of the diseases under consideration, center around the chemical, physiological, and biological laws of metabolism and function. Thus, the processes are confronted which are operative in the actions and reactions between substances in solution, and, as the living cell is an energy transformer possessing powers which no other type of transformer does, the fact must be ever remembered that, to employ the words of Hill, "the cell in structure consists of colloids and crystalloids in common solution in water." To quote further, we have to consider "The nature and action of the input and output of the cell, including its secretions and how these are produced; the osmotic phenomena and the effects of changes in the surrounding medium; the characteristic accompaniments of stimulation from part to part, and the effects produced by cells possessing a life in common, as in the multicellular animal.

"Physical chemistry affords us one of the most powerful experimental engines in conducting such inquiries, for the reason that the living cell is

in the structure a complex solution of both colloids and crystalloids, and that the chemical reactions occurring in the cell are reactions in solution. Accordingly, although the whole matter is profoundly affected by the fact that the *cell is alive*, it is evident that our knowledge of cellular activities must be based on knowledge of the properties of solutions, both of colloids and crystalloids; of reactions in solution; the velocity of such reaction, and the conditions of the equilibrium; of the mutual effects of crystalloids and colloids upon one another, when in common solution, and of the effects of the *living cell as a peculiar energy transformer upon osmosis and diffusion.*" This somewhat extensive quotation is imposed because there are included several laws and their phenomena which are frequently encountered in nutritional diseases, and upon which are based the principles of treatment.

Many of the phenomena which, upon superficial view, appear to be symptomatic of numerous and even diverse processes are, when more closely observed, found to be based upon a comparatively few fundamental principles. Thus, for example, ulceration and albuminuria are expressions only of degrees of practically but one process, *impaired nutrition* of the involved cells, and the resultant, diminished functional power and local death.

It may be well to allude here to that resistance of cells to adverse influences which renders them, for a time at least, immune to invasion, and to the maintenance of what is so aptly termed "physiological equilibrium," as well as to recall the fact that cells, doubtless, in some manner not yet understood, possess the power of emitting and sending messages to the proper sources calling for the supply of substances necessary for their integrity and life.

It must also be borne in mind that for a cell to be modified in its functionating powers it is necessary that there should enter into it some practically foreign substance. This may either catalytically exert a perverting influence, or, by forming compounds of less or greater degrees of stability, establish relatively easy or difficult dissociation products. Oxyhemoglobin and methemoglobin illustrate the point presented. In syphilis we have another example, and, as is well known, the combination, whatever it may be, of the toxins of the spirocheta with the protoplasm of the cell so alters its inherent functional properties as to cause the nutritional disturbances symptomatic of the disease. Empirically, it is known that, as a rule, unless mercury becomes associated with a syphilized cell, and some combination occurs with its protoplasm which activates an antagonistic influence, the structure is incapable of recovering its normal functions. When it is recalled that, with the exception of the splenic corpuscles and a few perivascular lymph-spaces of the central nervous system, the cells of the body are not in direct contact with the blood, and that structures such as the cornea, cartilage, skin, bone, and ligaments, and organs such as the heart, liver, and kidney, find their source of substances necessary to the life of the respective component cells, as well as those which are essential for function, in what is aptly termed the *intercellular fluid*, we have one of the most important fundamental principles underlying digitalis therapy presenting. Especially is this a fact when

it is remembered that the normality of the intercellular fluid *depends upon the mean pressure existing between the arterial system, on the one hand, and the venous, on the other.* Cells, therefore, as environed by this intercellular fluid, are comparable with areas of soil in a swamp.

The intercellular fluid serves three principal offices: (*a*) supplying the cells which it surrounds with substances necessary for the maintenance of cell life; (*b*) supplying the substances essential for the cells to functionate; (*c*) holding in solution the products resulting from the process of cell existence, and also the products of cell function. The reaction of the myocardial cells to the intercellular fluid beautifully demonstrates the phenomena of the physicochemical, biochemical, and physiological laws involved, which constitute the fundamental principles of digitalis therapy applicable to diseases of nutrition. The inherent vital property of contractility of the myocardial cell, after that beat which is the result of its response to the activating influences of the normal intercellular fluid, would not repeat itself if that medium did not almost instantaneously return to normal. It is conceivable that the reaction of the cell to the fluid resulted in the completion of a series of phenomena of a chemical and vital nature. Thus ions from the low molecular formula of crystalloids in solution found the potassium and calcium salts utilized, and, the products of cell action promptly entering the intercellular fluid, while the processes of osmosis and diffusion occurred, in a twinkling the functions of a given cardiac cycle were ready to be repeated because of the *renormalizing of the intercellular fluid*, if it may be thus designated.

The velocity with which these actions and reactions occur, as well as the specific nature of the involved crystalloids and colloids, constitutes a factor in tissue reactions characteristic of many nutritional disorders. Thus, congestion resulting in an intercellular fluid of either hypotonic or hypertonic properties determines, respectively, retrograde processes, on the one hand, or hypertrophic and hyperplastic, on the other. The reasons for this need not now be further elaborated. Sufficient has been presented to demonstrate that by maintaining a normal blood-pressure, *i.e.*, the circulatory equilibrium, the intercellular fluid must, other things equal, also be so maintained. If this be true, and the fact also that protoplasm and bioplasm are enabled thereby to maintain resistance to pathological influences, and even after being perverted, under favorable conditions, to show recuperative power, it logically follows that the *restoration of lost circulatory equilibrium* is a principle of treatment applicable to a vast field of nutritional diseases.

It must not be forgotten, either, that digitalis itself is a living cell, so to speak; that its inherent properties, like those of the normal living body, are the consequences of physicochemical, biochemical, and physiological laws, and that, like all living matter, it is subject to influences that result in a healthy product or the reverse. This may explain why drug agents offer for sale to pharmacists digitalis leaves varying in price from 40 cents to $1.20 per pound. Such a condition of affairs is applicable to the entire materia medica and is criminal. There should be but one standard of drug. In other words,

unless digitalis is cultivated, selected, and the preparations made under scientific and proper conditions and methods, it is, like any living organism, a creature of unreliable and uncertain potentials. Standardized preparations—and fresh ones only, because all rapidly deteriorate and lose strength—should be employed and, what the writer infinitely prefers, active principles of demonstrated therapeutic value. An experience of many years permits of but one conclusion, viz., that, wherever perverted circulatory equilibrium obtains, a digitalin of known reliability, administered in doses of from $\frac{1}{6}$ to $\frac{1}{2}$ grain three or four times daily, will, other things being equal, secure the desired results.

In the following respect this remedy is comparable with a food: Carbohydrates are essential for the maintenance of the processes of life, as are also hydrocarbon and proteid foods, and, since these are utilized, they must be supplied at regular intervals, and in sufficient quantities. So with digitalis. It is, in the sense outlined, a food, and in the nutritional diseases of senility, particularly, it must be "eaten" three times a day, as are our meals, so long as life lasts. Unfortunately it causes gastric derangement in some individuals in whom large doses are necessary to maintain circulatory equilibrium, and in these experience teaches that another derivative, digalen, or soluble digitoxin, proves invaluable. Again, the digalen seems to possess an especial power to restore lost tone of the veins, thus affording, in addition to its activity upon myocardial function, a means of bettering relaxed veins and emptying a turgescent venous system. The digitalin powerfully stimulates the propelling function of the arteries and the vasoconstrictor nerves—factors in lost circulatory equilibrium the actions of which need not be enlarged upon before this body.

It is evident that, in view of the certainty with which the administration of these two derivatives of digitalis (when reliable products are employed) is followed by the restoration and maintenance of circulatory equilibrium, we have in them invaluable remedies for assisting cells to resist the invasion of even the tubercle bacillus, or rather for aiding the infected cells to overcome the pathological condition. The writer has seen otherwise-failing treatment converted into success by adding digitalis therapy to the best *secundum artem* methods. Ununited fractures, ulcers, edema, effusions, and the albuminuria of passive hyperemia have promptly been overcome when, in addition to the usual therapeutic efforts, these remedies were added. The nutritional disorders secondary to passive hyperemia, and in turn the consequence of valvular and myocardial diseases, are in many instances after long periods of digitalis therapy practically controlled.

The reasons or explanations for these results are self-evident, from the brief presentation already given of the principles involved. The relief afforded in the psychical defects accompanying incipient senile cerebral retrograde changes, symptomatically indicated by insomnia, forgetfulness, failing memory, and difficulty of concentrating thought, which, in a word, constitute beginning inability to discharge duties, and so frequently threaten the loss of positions of great responsibility, supplies a group of cases which proves the correctness

of the solution of the problems submitted for your consideration. The writer has seen the catheter life of senile vesical paralysis overcome after months of digitalis therapy instituted for the purpose of re-establishing a normal intercellular fluid in the cord, as well as, perhaps, in the viscus itself. That such a result can be secured is proof of the correctness of the position assumed. It goes without saying that, if nutritional disturbance has existed sufficiently long to result in atrophy and death, nothing can be achieved, but if it has progressed only to the degree of "wilted, not withered, leaves," so to speak, restoration of an adequate flow of "sap" will find the foliage refreshed and invigorated; and this achievement is possible in many conditions too commonly regarded as beyond relief. Threatened cerebral "softening," progressive myocardial degeneration, and arterial nutritional disorders have all in the writer's experience been held in abeyance and improved far beyond the conditions obtaining when the patients were first seen. For many years the health and strength thus restored have been maintained by feeding, as with food, sufficient quantities of the two, thus far, best-known derivatives of digitalis already mentioned.

Their administration prolongs the diastolic pause and enables the varied processes of nutrition to take place and the myocardium to maintain its life and functional powers: the propelling function of the arteries—a function the importance of which is not yet appreciated—is greatly reinforced: the intercellular fluid is maintained in its normal condition, and the various physiological laws are afforded ample opportunity to operate, and the cell to exert its peculiar energy-transforming power by means of which that mysterious force, life, determines existence.

THE EFFECTS OF MEDICINAL DOSES OF ACONITE UPON THE PULSE RATE.

By R. D. RUDOLF, M.D. (Edin.), F.R.C.P., and C. E. C. COLE, B.A., M.B.,

TORONTO, CANADA.

The use of aconite as a medicine seems to date from 1762, when Baron Störck introduced the drug into practice. But aconite has been used by the laity from time immemorial, and few drugs have had a more varied history. Störck recommended the preparation as a diaphoretic and diuretic, and employed it in chronic rheumatism, gout, paralysis, phthisis, and a great variety of diseases. It was eagerly taken up by the profession, for some years was enormously used, and then fell into disuse. In 1796 Hahnemann experimented with it and recommended it in inflammatory fevers, where the allopathics would bleed. In 1835 M. Lombard, of Geneva, advocated its use as an anodyne and antiphlogistic in acute rheumatism and other acute local inflammations. "Under doses varying from ½ grain to 8 grains every two, four, or six hours, the severest attacks of febrile rheumatism yielded in the course of two, four, or six days; and even protracted cases of subacute rheumatism were often cured. The relief of pain and abatement of fever commenced in a few hours, without any critical evacuation by the bowels, skin, or kidneys" (Christison).[1]

It appears to have been Alexander Fleming who first drew attention to the action of the drug in slowing the cardiac rate. In 1845 he wrote a thesis upon the drug and showed how it slowed the heart's action. He described four stages, according to the amount given. After 5 minims of the tincture the heart was slowed; the pulse, some four hours after the administration, would have fallen some 8 beats. If a second dose were then given, or 10 drops had been given at first, the pulse would fall another 8 beats and have become weaker, though still regular. If two hours later 5 drops were again given the pulse would fall to perhaps half its normal rate, but still remain regular. In the fourth degree, after the taking of another dose of 5 drops, the pulse would become weak and irregular, and if the action of the drug were carried to a fatal extent the pulse would become gradually imperceptible. These results seem to be very remarkable until we realize that Fleming used a tincture which was some six times as strong as the U. S. P. tincture, and therefore about twelve times the strength of the B. P. tincture. He made it by passing 24 fluidounces of rectified spirit through 16 ounces of powdered aconite root, while the U. S. P. tincture is 1 in 10, and the B. P. tincture about 1 in 20. Thus Fleming used doses corresponding to ½ to 1 dram of the U. S. P. tincture, the maximum officinal dose of which is 15 minims, and for repeated doses 1 to 5 minims.

Ringer and Murrell next introduced the employment of very small but

frequently repeated doses, and under the influence of the former's book (passing through its many editions) this method of using the drug became very widespread, although of late years one does not hear so much of it. Ringer specially recommended its use in the treatment of inflammations accompanied by fever, and indeed said: "In the treatment of inflammations, the thermometer and aconite should go hand in hand."[2] He gave ½ to 1 drop (of the B. P. tincture) every ten minutes for two hours and then every hour, and such is the usual suggestion that echoes through most of the text-books to the present day. Under such treatment the pulse is believed to become slow, the fever to lessen, and the skin to become moist.

But, in the doses recommended in the pharmacopeias, and still less in those suggested by Ringer and Murrell, the pulse does not seem, according to our observations, to be at all affected. With any other effects we are not here concerned.

One fact that stands out with great clearness is that aconite in sufficient amounts is a violent poison, acting powerfully upon the circulation, and finally killing by paralyzing the respiratory center. Thus 1 c.c. of our solution of the crystalline aconitine (0.0225 per cent.—the strength of the B. P. tincture) killed a guinea-pig in a few minutes. In less powerful, but still large, doses it has a marked action on the heart, slowing it, chiefly through the vagus. But, as said, in doses such as are recommended in the pharmacopeias, and especially in the fractional doses introduced by Ringer and Murrell, the effect upon the circulation is *nil*, according to our findings. These negative results, of course, may have been due to either of two causes: (1) the tincture used in the experiments was weak or inert, or (2) the doses were too small to have any appreciable effect.

F. W. Price found that several, in fact all, the samples that he obtained from reputable druggists in England were inert, when tested in Professor Cushny's laboratory. He then obtained a standardized preparation from this laboratory, and still found that the drug, even in doses far larger than those recommended in the British Pharmacopeia, had no effect upon the pulse rate, and, rather as a side issue, had no influence upon the blood-pressure. These results were embodied in a paper which he presented before the British Medical Association last year.[3] At that time one of us ventured to express the opinion in discussion that small, repeated doses of the tincture (say 1 or 2 minims every fifteen minutes) had a marked effect in acute febrile conditions such as tonsillitis, it seeming to slow the pulse and produce perspiration. During the past year the writers have tested the drug as regards the effects upon the pulse rate in many cases, always using medicinal doses, and this paper gives the results of our work.

To commence with, we used the ordinary B. P. tincture which was in the Toronto General Hospital, and which had been obtained, as we afterward found, from three reputable firms of wholesale druggists. The pulse rate was usually taken for some hours both before and after the administration, and in many cases the blood-pressure was also measured, but no effect upon the circulation was detected. Often considerable fluctuations were seen, but

it was found that these were mere coincidences and were just as apt to occur without the aconite. After finding no effects from the administration of the hospital tinctures we wrote to a well-known drug firm and they kindly forwarded a quantity of B. P. tincture "which has been tested both physiologically and in the laboratory and which we guarantee is of B. P. strength." Most of our experiments were done with this tincture, and were still negative. Then we got Dr. V. E. Henderson, associate professor in charge of the Pharmacological Department of the University of Toronto, to test this tincture, and he reported it as very weak. The bottle had stood in a room at about 60° F. for some three months before he tested it, and probably had depreciated since we first got it. Next, the same firm kindly sent us some pure crystalline aconitine, which Dr. Sharpe, of the Pharmacological Department, found by experiments on animals to be of full activity. He was good enough to make for us a solution of it corresponding in strength to the B. P. tincture, viz., 0.0225 per cent., and we continued our experiments with this solution,—still with negative results.

Our experiments were done, as will be seen from the table below, upon two classes of patients: (1) those with normal pulses, and (2) those with abnormally frequent pulses. Some of the latter had fever and some had normal temperatures. In none of them (51 in all) was any decided effect upon the pulse rate observed. Occasionally the pulse would be found to be slow after the taking of the drug, but when the pulse was watched for hours before and for hours after the administration it was seen that such fluctuations occurred without any aconite. The psychic effect of the administration, with the frequent taking of the pulse, must be taken into account. In 1 case of persistent tachycardia, following typhoid fever, the pulse dropped some 40 beats for twelve hours after small, repeated doses were given, which looked like a marked effect, but when the experiment was repeated upon the same individual under exactly the same conditions no such result, or rather sequence, occurred.

It appears, from both Dr. Price's findings and our own, that the tincture of aconite on the market is usually inert. We have discussed this matter with Dr. McGill, chief analyst to the Inland Revenue Department of Canada, and he hopes soon to examine samples from various parts of the Dominion. The results will be interesting. The difficulties of testing the drug, however, are great. The aconite root contains at least three active principles—*aconitine, aconine*, and *benzaconine*—and although it is an easy matter to assay the total alkaloids, it is very difficult to find the proportion of aconitine. Yet it is upon this alkaloid that nearly the entire action of the root depends. A simpler test, and one which is chiefly employed by the manufacturing houses, is the "Squibb test." This depends upon the fact that aconitine, and it only, produces, when applied to the tongue in great dilution, a tingling. A solution of 1 in 500,000 of aconitine will give this reaction. A solution of 1 in 70 of the American tincture or 1 in 35 of the B. P. preparation acts similarly. A dram of the dilution is held in the anterior part of the mouth for exactly one minute and then is discharged. A distinct tingling should be perceived

within ten to fifteen minutes. Mr. F. O. Taylor, who has written very fully upon the tests for aconite,[4] believes that this is the best practical test that we possess. None of the tinctures that we procured gave this reaction, but the solution of crystalline aconitine, which was of the strength that the tincture should be, and was then diluted as described, gave it very distinctly. This same solution, however, only gave the Squibb reaction when four times as strong as three months before, thus showing how apt it is to depreciate with keeping.

But even when the drug is active, small doses seem to have no effect upon the pulse rate. How, then, may we explain the reports to the opposite effect which teem in medical literature, and which support the advice found in nearly every textbook of therapeutics and medicine? To our minds it is another example of the *post ergo propter* fallacy, which fallacy is so often seen in medicine and has so often been responsible for many findings which further trial has shown to be without foundation—something is given and the patient improves: *ergo,* the improvement is due to the something given.

The examples of marked and even dangerous effects obtained from small medicinal doses of aconite which are occasionally chronicled can be due only to one of two things: (1) either there has been some mistake in the dispensing or administration of the drug, so that the patient has received far more than was intended, or (2) an idiosyncrasy must exist, so that toxic effects are obtained from a dose which ordinarily has no effect. For example, Woodbury[5] records a case of nearly fatal poisoning from 3 drops of the tincture. No doubt, as Shoemaker says,[6] the toxic dose and the susceptibility to aconite both vary greatly in different subjects.

It can truly be said that the theme of this paper is destructive rather than constructive, but surely the subject of therapeutics almost more than any other part of the domain of medicine requires destructive criticism in order that we may clear away the chaff and thus make more clear the valuable parts that remain. The pharmacopeias of old contained many weird substances, such as human urine, which were gravely prescribed by earnest men, and good followed; and yet we do not believe nowadays that that good resulted from the remedy used. And the pharmacopeias of today contain many substances which might well be left out, and we believe that aconite, certainly in the doses recommended, is one of these.

As already said, aconite, when given in massive doses, is an extremely powerful body, and it may be of great value where it is desired to slow the pulse or obtain some of its other effects, but this paper is not dealing with such use of the drug at all.

Dosage of B. P. tincture.	Condition of patients.	Age.	Effects on pulse rate.
One minim every ten or fifteen minutes for 8 to 10 doses.	8 convalescents with normal pulse rates		nil
	8 convalescents with frequent pulses.		nil
	Posttyphoid tachycardia	25	nil
	Posttyphoid neuritis	45	nil
	2 healthy orderlies		nil
	Tuberculous knee	20	nil
	Typhoid fever	22	nil

Two minims every ten to fifteen minutes for 8 to 10 doses.	Acute tonsillitis	23	nil
	Hysterical vomiting	21	nil
	Cholecystitis	50	nil
Three minims every ten to fifteen minutes for 8 to 10 doses.	Convalescent typhoid	25	nil
	Gall-stones	28	nil
	Rheumatoid arthritis	23	nil
	Streptococcic septicemia	24	nil
	Pleuropneumonia	55	nil
	Septicemia	24	nil
	Convalescent pleurisy	28	nil
Four minims every ten minutes for 8 doses.	Pleuropneumonia	25	nil
	Do. repeated		nil
Four and a half minims every ten to fifteen minutes for 8 to 10 doses.	Phthisis pulmonalis	30	nil
	Convalescent typhoid	25	nil
	Rheumatic arthritis	60	nil
	Hysteria	22	nil
Two minims every hour for 4 doses.	Convalescent typhoid	25	nil
Three minims every hour for 10 doses.	Convalescent typhoid	25	nil
	Tuberculosis	30	nil
	Mitral stenosis	22	nil
	Gall-stones	22	nil
	Arthritis deformans	21	nil
Four and a half minims every thirty minutes for 10 doses.	Tuberculosis	30	nil
Six minims every hour for 10 doses.	Posttyphoid neuritis	45	nil
	Arthritis deformans	22	nil
Ten minims every hour for 10 doses.	Exophthalmic goiter	18	nil
	Splenomyelogenous leukemia	45	nil
	Chronic rheumatism	25	nil
One dose of 15 minims.	Neurasthenia	21	nil
	Rheumatoid arthritis	25	nil

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SYMPOSIUM ON THE ETIOLOGY AND TREATMENT OF HIGH BLOOD-PRESSURE.

THE ADRENALS AND THE BLOOD-PRESSURE IN THEIR RELATIONS TO ARTERIOSCLEROSIS.

By CHARLES E. de M. SAJOUS, M.D., LL.D.,

PHILADELPHIA, PA.

The functional relationship existing between the adrenals and the blood-pressure through the direct action of the secretion of these organs upon the muscle-fibers of the heart and arteries, as demonstrated by Oliver and Schäfer, has now become classic. It is clearly established also that the terminal arterial ramifications which supply the capillaries, the arterioles, receive the brunt of the contractile action of the adrenal product. This action is not limited to any particular organ; it is quite general, as demonstrated by plethysmographic observations of the extremities, kidneys, spleen, etc. In the ten minutes to which I must limit my remarks, owing to the many papers which form this symposium, I shall be able to submit for discussion only one of the morbid effects this action of the adrenal secretion on the arterioles may entail: arteriosclerosis.

The production of vascular lesions resembling, at least, those of arteriosclerosis by injections of epinephrin is a familiar fact of experimental medicine. First observed by Josué, this phenomenon has been witnessed by many other investigators. Some of these, Lissauer for example, have argued that the lesions differed from those of typical arteriosclerosis, and that they rather approximated those of syphilitic angiosclerosis; but when we recall that syphilis is one of the important etiological factors of arteriosclerosis, it seems clear that Lissauer's view is hardly well founded. Again, it was found by Miles that there was no constant relationship in rabbits between the extent and frequency of the lesions found and the size and frequency of the doses administered; but doubtless, here age, vigor, size, and other individual peculiarities prevailed in the different animals to modify more or less the effects of the drug. Nor is the occurrence of the spontaneous degeneration noted by Miles and Johnstone a valid objection; it only shows that rabbits, like man, are subject to the disease, a fact which places its artificial production on a sounder basis. These few examples will suffice to sustain the point I wish to make in this connection, to wit, that even the various objections that have been recorded against the validity of Josué's opinion tend to show that the active principle of the adrenal secretion can produce lesions which are at least very similar to the familiar lesions of arteriosclerosis. Thus, as stated

by Guthrie McConnell very recently: "The changes which develop do not correspond accurately with those of the ordinary nodose sclerosis, but they are, however, indistinguishable from the changes seen in Moenckeberg's type of medial degeneration. There is the same atrophy of the muscle-fibers and giving way of the media with the production of pouchings, which at times are so extreme as to become definite, small, sacculated aneurisms. There is a fatty, followed by a calcareous, degeneration of the elastic tissue elements of the coat."

Remaining strictly within the field of the pathogenesis of the disease, we are brought to inquire into the manner in which it is produced in man through the adrenals in the light of the above facts, and with the generally recognized causes as pathogenic factors.

Thayer's[1] series of 3894 cases studied in Osler's wards gave heavy work, alcoholism, rheumatism, diphtheria, scarlet fever, syphilis, malaria, and pneumonia as the most important factors in the order of their enumeration, heavy work being represented by 62.2 per cent. In Huchard's[2] series of 1835 cases the predominating causes were, in the order of their importance: gout, rheumatism, syphilis, the abuse of tobacco, infectious diseases, diabetes, alcohol, and malaria. Brooks's[3] series of 400 cases gave occupational lead poisoning, severe manual labor, alcohol, nephritis, syphilis, and tuberculosis as the conspicuous causes, their importance decreasing in the order named. These statistical figures, based on an aggregate of 6129 cases in various parts of the world, suggest a toxemia as the common pathogenic factor of the disease —specific toxins where infectious diseases are the causative agents; excessive metabolism and tissue waste products in hard physical labor; purin bases in the gouty, as well as in the cases due to chronic lead poisoning, which, as believed by Frank S. Billings, promotes a condition akin to gout with nephritis as a complication. All these main causes of arteriosclerosis, when reduced to their simplest expression, can thus be summarized by this one word: intoxication, as long ago emphasized by Traube and Rokitansky.

What is the relationship between this general toxemia and the adrenals?

Suggestive in this connection is the fact that all but one of the morbid conditions (the exception being alcohol, which has not been studied in this connection) known to provoke arteriosclerosis have also been found to cause overactivity of the adrenals.

Prominent, we have seen, is the excessive physical labor, which in Thayer's statistics stood first in the list as the cause, with over 62 per cent. of the 3894 cases studied. Now, Abelous and Langlois[4] twenty years ago showed conclusively that the internal secretion of the adrenals destroyed fatigue products, *i.e.*, toxic wastes generated during muscular activity. This has been confirmed by Mosse[5] and others. That arduous and prolonged muscular labor should under these conditions entail overactivity of the adrenals is self-evident. Febrile infections, so prolific collectively as a cause of arteriosclerosis, are also known to promote abnormal adrenal activity. Diphtheria toxins, for example, were found by Wybaux[6] to produce marked hyperemia of the adrenals, which when excessive leads to destruction of the organs. Is this due to a

local toxic necrosis or to excessive stimulation by the toxin? This is answered by the fact that the prolonged use of diphtheria toxins in small doses by Langlois and Charrin[7] in guinea-pigs produced not degeneration of the adrenals, but hypertrophy—so marked, in some instances, as to cause these organs to attain four times their normal size. Petit[8] noted the same phenomenon in fishes; Stilling,[9] in rabbits; Auld,[10] in cats. Roger[11] obtained the same hyperemia—sufficient in some instances to produce adrenal hemorrhage—in guinea-pigs with the pneumococcus, and Langlois,[12] with the *Bacillus pyocyaneus*. The excessive production of adrenal secretion during the prevalence of these toxemias is further shown by the post-mortem exhaustion of the active adrenal principle noted by Bainbridge and Parkinson[13] with the aid of the chromaffin test and also by Luksch,[14] who employed as test-criterion the relative pressure-raising power of extracts prepared with the organs of subjects in which death had been due to uremia, phosphorus poisoning, and infectious diseases. As to the influence of excessive smoking, Cannon, Aub, and Binger[15] have recently found experimentally that "nicotine in small amounts (0.0035 to 0.0075 Gm. in cats) caused an augmentation of adrenal secretion."

This evidence is further sustained by the fact that Coplin,[16] in an histological examination of the adrenals of 22 cases of arteriosclerosis, found that 17 were markedly altered, the exceptions being the seat of a tuberculous process in 3 instances and of a secondary neoplasm in 1. Again, potassium iodide, our best remedy in arteriosclerosis, has been found by Vernulet and Dmitrowsky to inhibit the secretory activity of the adrenals. On the whole, the causal relationship between overactivity of the adrenals induced by the various toxics enumerated and arteriosclerosis seems clearly defined.

We are thus brought to attribute to adrenal overactivity, in the production of clinical arteriosclerosis, a process similar to that caused by Josué when he injected epinephrin experimentally. What is the nature of this process?

We have seen that the predilection of the adrenal product for the arterioles is generally recognized. In other words, whether we inject epinephrin or whether the adrenals are overactive, what effects are produced on the vascular system *per se* are borne directly by these terminal arteries. This appears to me to furnish the key to the situation, or rather the missing link of a chain of facts which clearly explain the pathogenesis of at least the familiar forms of arteriosclerosis from beginning to end. Indeed, the arterioles being the channels through which the vasa vasorum are connected with the general arterial circulation, any condition capable of reducing the caliber of the former—the arterioles—reduces in proportion the volume of arterial blood they supply to the vessel walls through these minute nutrient vessels, the vasa vasorum. If this deficient nutrition of the vascular tissues is continued sufficiently long, they become necrotic or atheromatous and ultimately sclerotic, mainly around their nutrient vessels. We have the testimony of Councilman to this effect, this pathologist having found that "in the circumscribed or nodular arteriosclerosis the primary alteration consists in a degen-

eration or a local infiltration in the media and adventitia, chiefly about the vasa vasorum." Cowan[17] noted, in fact, that vasal changes were sometimes the only visible lesions, and he refers to cases in which "the interference with the vascular supply from the vasal vessels produced medial and intimal necrosis."

Summarizing the foregoing data, all of which are based on clearly defined experimental and clinical observation, I would submit that the interposition of the adrenals and the contractile action of their secretion upon the arterioles in the problem enable us clearly to understand the manner in which so many forms of intoxication can cause arteriosclerosis. Briefly, the pathogenic toxic, whatever it happens to be, causes a more or less violent overactivity of the adrenals (probably by exciting their center) and thus increases sufficiently their secretory activity to reduce more or less the caliber of the arterioles from which the vasa vasorum receive their supply. Deficiently nourished through these their nutrient vessels, the medial and intimal vascular tissues degenerate, forming the familiar sclerotic patches.

This may not represent the sole pathogenetic chain of events,—indeed, I believe that autolysis, through the presence of an excess of antibodies in the blood, may engender what might be termed an acute form of arteriosclerosis in certain febrile infections, typhoid fever and acute rheumatism, for example, —but it does, in my opinion, include the vast majority of cases we meet in everyday work.

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THE NATURE OF THE CARDIOVASCULAR CHANGES IN NEPHRITIS.

By ALFRED C. CROFTAN, M.D.,

CHICAGO, ILL.

In attempting to interpret the cardiovascular lesions occurring in association with nephritis, it is important to remember that, on the one hand, many cases of nephritis run their whole course without the appearance of any cardiovascular manifestations whatsoever, whereas, on the other hand, cases of nephritis occur in which increased blood-tension makes its appearance within forty-eight hours after the onset of the renal difficulty and rapidly leads to organic cardiac and arterial lesions that proceed throughout the course of the disease.

One can hardly say that any particular form of nephritis, using the orthodox textbook classification, is accompanied by cardiovascular changes and any other form not. I have gained the impression that it is particularly those varieties of nephritis in which the glomeruli are primarily involved, or in which the glomeruli participate in a pan-nephritis, that become complicated by cardiovascular changes.

It is difficult to explain this sequence of events. Hypothetically one might postulate that the glomeruli are intended to excrete certain pressor principles and that in disease of the glomeruli these principles are retained, high tension and cardiovascular changes being thus produced. But a much more seductive explanation, based on physiological reasoning, is the following: The excretion of urinary end-products through the glomeruli is a true process of filtration and a function of the blood-pressure, or, by implication, of the rapidity of the blood-flow through the glomerular arterioles; whereas the excretion of urinary end-products through the epithelia of the tubules is a glandular process of secretion. In destruction of the glomerular tissue, therefore, any attempt on the part of the organism to compensate for this deficiency implies the production of increased blood-pressure in the remaining intact glomeruli. This is brought about, as a rule, by an increase of the general blood-pressure throughout the body. Such a process, therefore, while conservative and compensatory, and hence useful as far as the renal function alone is concerned, may become deleterious and dangerous in respect of the organism at large.

In interpreting the origin of the cardiovascular changes following nephritis, it is important to establish where and how they arise. The first, the most constant, and the determining feature is high blood-pressure. If this persists for a period of weeks, it is followed, first, by an hypertrophy of the left heart, later by an hypertrophy of the right heart, and, finally, by arterial degeneration.

The increased blood-tension may originate either from the blood itself, from the heart, or from the arteries.

The only factor that could lead to an increase of the blood-pressure through the direct agency of the blood (not including, of course, the rôle of the blood as a carrier of toxic urinary pressor principles) would be an increase in its viscosity, and, hence, in its friction. Viscosity determinations in cases of nephritis accompanied by high blood-pressure have, however, revealed no constant deviation from the normal.

The heart might lead to increased blood-pressure, either by an increase of the systolic volume or by a shortening of the systole. The heart's rapidity is, however, not uniformly increased in the disorder under discussion. Nor is there any evidence to show that more blood is expelled with each systole than normally.

The most rational explanation is narrowing of the arterial lumen, either in some of the large vessels or in many of the smaller ramifications of the arterial tree, or in both. Even slight narrowing of the arterial lumen, *i.e.*, slight arterial contraction, would, according to well-known physical laws, promptly lead to a great increase of the general arterial blood-pressure. I do not believe that this narrowing of the lumen is generally due to organic changes in the vessel walls, at least not in the beginning. It is probable that in many cases the changes are secondary to persistent high tension. Presumably we are dealing with a functional narrowing of the lumen, the result of an increased vasomotor tonus. Vasomotor instability is one of the most characteristic postnephritic manifestations.

All these considerations concern only those forms of cardiovascular degeneration that occur consecutively to nephritis. There remains a large number of cardiovascular disorders in which blood-pressure changes either precede or accompany nephritis. Logically one can distinguish three possibilities, to wit:—

1. The cardiovascular changes precede the nephritis and cause the latter. This, I believe, is the sequence of events seen in true Bright's disease; for in many of these cases high tension is observed to be present long before nephritic symptoms appear. The manifold causes of this high tension need not be discussed here. A persistent increase in the arterial blood-pressure in this group of cases ultimately leads to degenerative changes, particularly in those organs of the body that are supplied by end arteries, viz., chiefly the brain, the retina, and the kidneys; hence we not infrequently witness instances of high tension accompanied by certain cerebral symptoms and a retinitis "albuminurica," in which the renal manifestations are at first completely absent or only develop at a late period of the disease.

2. The cardiovascular changes develop simultaneously with the nephritis. Here some agency must be operative that affects both the cardiovascular apparatus and the kidneys at the same time. To this category belong chiefly the cardiorenal disorders seen in chronic lead poisoning and, above all, in the so-called "gouty diathesis."

3. The cardiovascular changes are manifestly of renal origin, consecutive to the nephritis and in all probability due to renal inadequacy with retention of toxic urinary pressor end-products. This is the most common sequence of events, and has been discussed above.

It will be seen how important it is from the standpoints of prognosis and of treatment to attempt, in each case of nephritis complicated by cardiovascular disorders, an interpretation of the sequence of events.

HIGH BLOOD-PRESSURE ARISING FROM NERVOUS STRAIN IN DISEASES OF THE NERVOUS SYSTEM.

By EDWARD D. FISHER, M.D.,

Professor of Mental and Nervous Diseases in the University and Bellevue Hospital Medical College,

NEW YORK, N. Y.

THE various conditions of blood-pressure in diseases other than nervous have been fully discussed in this symposium. In looking into the subject from my special standpoint, I would emphasize the fact that many of the conditions already referred to are present and complicate the special disorders of the nervous system which I shall discuss; indeed, may be factors in their etiology. They may exist alone, independently, but it is more common to find them coexisting. I shall refer in this paper especially to disorders of the nervous system due to arterial disease, either endarteritis of the atheromatous type or that consequent on syphilis, to cerebral compression as caused by new growths, increase of cerebrospinal fluid, etc., or, again, to vascular changes the result of the direct poisons, as in uremia, diabetes, alcoholism, etc.

In the first group, endarteritis of a degenerative character, we find a rather general distribution of arterial disease. Hence not only is the nervous system involved, with resulting symptoms of cerebral and spinal nature, but a condition of interstitial nephritis and cardiac hypertrophy is also present. This is the usual picture in those past 40 years of age who are the subjects of apoplectic or epileptic seizures. In the young cases, with probably acute cardiac and renal involvement, we have symptoms peculiar to the disorders of the special organs, but little or no tendency to cerebral hemorrhage or apoplexy. The blood-pressure in these cases may be temporarily high, but is not continuously so, and is more easily relieved or controlled.

In the former cases, however, with a general endarteritis, including involvement of the cerebral vessels, we have a constantly high blood-pressure, subject also to marked increase; which is the danger point, indicating the probability of a seizure, apoplectic or epileptic. In an interesting case corresponding to this type the whole course of the attack could be marked out by the rise of blood-pressure while an examination was being made with the sphygmomanometer. The pressure continued to rise until the patient passed into an epileptic seizure, the cessation of which, on the other hand, was marked by a rapid fall in the pressure. In a not dissimilar case reported by Pal, contraction of the arteries in the eye and stasis with dilatation of the veins were observed. In these two cases we have explained, very probably, the actual state of the circulation and the cause of the epileptic seizure. This condition marks out positively the difference distinguishing epileptic seizures of this nature from those which, for want of a better name, we still call idio-

pathic or essential epilepsy, and, again, from those due to a focal lesion, such as a tumor, meningeal disease, or trauma. Convulsions due to any cause, if violent or constantly repeated, will or can, from the exhaustion of the cortical cells, lead to mental disease; but the general mental complex is very different from the epilepsy beginning in childhood without a definite etiological factor, and explainable only on the basis of some cell degeneration of an hereditary nature.

In eclampsia during pregnancy a great and often sudden rise of blood-pressure is observed preceding the seizure. This evidently is not due to arterial disease, but to some toxic agent with which we are as yet unacquainted. The very suddenness of these seizures is their especial danger, and it is this type also which is the least easily controlled. High blood-pressure when present during pregnancy should be considered a danger signal.

In syphilitic endarteritis the blood-pressure is often very low or normal; if it be high, this is due, not to the arterial disease, but to complications such as nephritis, cardiac disease, or diabetes, etc. This probably explains the clinical condition, which is the result not, as a rule, of cerebral hemorrhage, but of cerebral thrombosis, as we know it is the cerebral vessels that are especially vulnerable to syphilis. The explanation of cerebral hemorrhage, or apoplexy, or epilepsy in these cases is a cerebral anemia, gradual in onset and often, though it is not permanent, depending, not on spasm in the arterial coats, but on a gradual, more or less complete occlusion of the caliber of the vessels from actual thickening of their coats, both intima and adventitia, or, again, as is often the case, on actual infiltration of new growth, syphilitic tissue or gumma, into the vascular walls, likewise causing occlusion of the lumen. As previously stated, we may in syphilitic cases have the other complications which modify this picture—explainable, as in non-specific cases, on the basis of either exogenous or endogenous causes. As might be expected, specific cases are more subject than others to these outside influences.

One is inclined, in studying his patients, after finding one factor suggestive of a given disease, to try to make any symptom fit into this special diagnostic feature, forgetting that probably other factors are also present which, if not the fundamental, basic cause of the condition, are exciting causes, removal of which may lead to a much more successful treatment of the fundamental disorder. Thus, we may, for example, have a hysterical paralysis; but this does not preclude the possibility of there being present at the same time an organic paralysis of either cerebral or spinal origin.

I have dwelt thus long on high pressure in vascular diseases of the nervous system because it is of greater importance in these conditions and more frequently diagnostic in character than in other nervous affections.

In cerebral growths there occurs compression of the brain, which may also manifest itself by high blood-pressure. Here, again, we have variations dependent on exciting conditions, such as cephalalgia, intercurrent disease of the kidneys or heart, drugs, etc. The convulsions present may be due to anemia from pressure, especially so in the case of general convulsions, and not improbably even in focal seizures. In the latter, however, it is possible

to conceive of seizures of the Jacksonian type being occasioned purely by irritation, such as can be mechanically induced experimentally by passing a faradic current through a given area. Abscesses or tumors often lead to low blood-pressure, except during certain seizures indicating local or general cerebral irritation.

There may be high blood-pressure in cerebral tumors, in hydrocephalus, or in compression following trauma. This high blood-pressure may be observed to fall as soon as the skull is opened, or more certainly on opening the dura, with the escape of the cerebrospinal fluid. This is not always true, however, in decompression operations following trauma; many such cases continue to show high blood-pressure and fail to regain consciousness.

Taking the blood-pressure as a matter of routine during cerebral operations is valuable, as a rapid fall indicates the need of stimulation or cessation of further extension of the operation at the time.

A very singular case of general high blood-pressure, involving both the splanchnic system and the cerebral circulation, was observed in a patient of 65 with interstitial nephritis of a mild character and arteriosclerosis. The initial symptoms were those of intense pain in the back and lower extremities, with paraplegia: the former were relieved by morphine. Within a few hours a distinct apoplectic seizure, with coma and right hemiplegia and aphasia, took place. The paraplegia and pain ceased, but the hemiplegia and aphasia remained.

In closing this brief paper, I would emphasize the value of observing the blood-pressure in all cases of vascular disease. Its sudden or steady rise will indicate the line of treatment which may avert a catastrophe, or, at least, it will inform us of the danger to our patient.

HIGH BLOOD-PRESSURE IN THE TOXEMIAS OF PREGNANCY.

By D. J. EVANS, M.D.,

MONTREAL, CAN.

My material consists of 38 cases of pregnancy complicated with eclampsia, albuminuria, and vomiting of a toxic type. In 12 of the series the toxic condition was severe enough to call for the interruption of pregnancy. In all the other cases, except those specially mentioned, labor occurred spontaneously. The Riva-Rocci instrument, or else the Tycos, was used in making the blood-pressure estimations.

Convulsions.

In 8 cases eclamptic convulsions occurred. In these there was no maternal mortality, though 1 of the cases developed symptoms of cerebral tumor as she was recovering and was removed to the Royal Victoria Hospital, where she died after operation. The child was born alive. Four children in these cases were born dead or died soon after delivery.

The highest blood-pressure recorded in this series was 200 millimeters and the lowest 140 millimeters. Immediately before the convulsions the blood-pressure was between 170 and 190 millimeters in most of the cases. One patient of this series had three convulsions, though her blood-pressure never rose above 150 except at the actual time of the convulsion. Two cases of this series had a blood-pressure of 200, one with five and the other with eighteen convulsions. The child of the former died of convulsions fourteen hours after spontaneous delivery.

Vomiting.

There were 4 cases of severe vomiting complicating pregnancy: 2 early in pregnancy and 2 near term. In the latter the blood-pressure was 140 in one, and 125 in the other. In both of these cases labor was natural and the children born alive. Of the former, 1, whose blood-pressure was never above 125, recovered from her vomiting and went to term; while the other, a most severe case, was aborted at the sixteenth week and died ten days later. This case was peculiarly interesting, for the blood-pressure, taken several times weekly for some time, was never found over 110, and was usually about 100; yet she developed retinal hemorrhages, in addition to other signs of severe toxemia. She was delirious for eight days before death, and the *post mortem* showed the characteristic liver changes present. The brain was very edematous. The pituitary gland was markedly enlarged and cystic, and contained several small hemorrhages.

Albuminuria with Toxemia.

Of the remaining 26 cases, all were albuminurics with toxic symptoms of more or less marked severity. Seven of these had a blood-pressure record of

160 millimeters or over, 2 of them recording as high as 180 millimeters. In 3 of them labor was induced on account of the severity of the toxic condition. In 12 of this series the blood-pressure was 140 or under, the lowest record being 120 millimeters. In this case labor was induced at the thirty-seventh week on account of the degree of albuminuria present.

Conclusions.

As a result of my experience I am inclined to conclude that the blood-pressure record is of little value as indicating the degree of toxemia present in cases of vomiting in pregnancy. Further observation would show that in this class of cases the blood-pressure falls below normal.

I have been surprised at the comparatively low reading obtained in many cases where the symptoms indicated the presence of a very considerable degree of toxemia. In 3 of my series induction of labor was imperative, though the blood-pressure was 150 millimeters, or under. In 4 cases with a blood-pressure exceeding 150 millimeters the toxic symptoms were so slight that the cases were permitted to go to term, and were delivered after natural labor.

I am inclined to consider the danger limit as 160 millimeters. In cases where, in spite of treatment, the toxic symptoms do not yield and the blood-pressure is maintained at or above this point, labor should be induced.

In cases of pregnancy with high blood-pressure without toxic symptoms, and I have met with several, there is little occasion for anxiety.

In all cases of pregnancy with hepatic or renal insufficiency the blood-pressure should be carefully observed. A rising blood-pressure in these cases, associated with other toxic symptoms, is indicative of danger, and 160 millimeters of pressure I consider the danger limit.

FACTORS WHICH ALTER BLOOD-PRESSURE IN PULMONARY TUBERCULOSIS.

By FRANCIS MARION POTTENGER, A.M., M.D.,
Medical Director of the Pottenger Sanatorium for Diseases of the Lungs and Throat,
MONROVIA, CAL.

The blood-pressure of an individual depends upon the power of the heart, the resistance met by the blood-stream in the peripheral vessels, the condition of the walls of the vessels, and the total quantity of blood, together with its distribution in the various vessels.

These various factors are in a state of equilibrium in healthy subjects and produce a certain resultant, the normal blood-pressure. Blood-pressure varies considerably in individuals in health, being influenced by many factors, such as age, habits of life, time of day, taking of food, climate, and meteorological conditions.

There is considerable personal error in determining blood-pressure, so that it is somewhat difficult to compare the individual readings made by different observers. This error should, indeed, be the same in all readings taken by the same individual; but since the error in the case of different observers is unequal, the results of different observers can only be compared in a relative way.

The following observations will illustrate this point: Statistics on blood-pressure in tuberculous patients gathered from different observers show wide differences in the results as measured in millimeters of mercury, but agree in one respect, viz., that the blood-pressure is lowered in this disease and becomes permanently lower as the disease advances. Strandgaard[1] took observations on 336 men and 286 women suffering from pulmonary tuberculosis with the following results, according to stages:—

I Stage	125 mm. Hg.
II Stage	121 mm. Hg.
III Stage	118 mm. Hg.

Burckhardt,[2] making his examination at Basel, found

I Stage	107.6 mm. Hg.
II Stage	104.6 mm. Hg.
III Stage	100.3 mm. Hg.

Igersheim[3] found

I Stage	100.4 mm. Hg.
II Stage	97.3 mm. Hg.
III Stage	95.4 mm. Hg.

Pottenger[4] examined twenty normal persons and compared the findings with those in 135 tuberculous patients divided according to stages of the

disease. The results were as follows, for both the systolic and diastolic pressures:—

	Systolic.	Diastolic.
20 Normal individuals	120	108 mm. Hg.
11 Patients in I stage	106	78 mm. Hg.
21 Patients in II stage	108	81 mm. Hg.
103 Patients in III stage	103	75 mm. Hg.

Thus we have average blood-pressures ranging as follows:—

I Stage	from 100.4 to 125 mm. Hg.
II Stage	from 97.3 to 121 mm. Hg.
III Stage	from 95.4 to 118 mm. Hg.

While there is a wide variation in the readings for the same stage of the disease as recorded by the different observers just quoted, yet there is general agreement on two points: First, that there is a lowered pressure in pulmonary tuberculosis, and, second, that it is lower in advanced tuberculosis than in the early stage.

In tuberculosis there are many forces associated with the disease which affect the blood-pressure. An analysis of these forces may help in better understanding the clinical manifestations of the disease.

It has been known for a long time that tuberculosis is accompanied by low blood-pressure, the reason generally assigned being the action of the toxins in producing vasodilator effects. Careful study and observation show, however, that this is not the only factor operating to produce low pressure, and, indeed, that it is only one of a number of factors which are influencing the blood-pressure in tuberculosis.

In the paper quoted above, I drew the following conclusions regarding blood-pressure in pulmonary tuberculosis:—

1. A relative low blood-pressure is found in tuberculosis, especially in advanced tuberculosis.

2. The factors which favor low pressure are the effect of the toxins upon the vasodilators, the weakness of the heart muscle, and general wasting.

3. The factors which have a tendency to maintain pressure are hypertrophy of the heart muscle and thickening of the systemic arteries.

4. Thickening of the systemic arteries occurs perhaps as a result of the action of toxins on the vessel wall, and, therefore, is found especially in patients who have had tuberculosis for some time.

Further experience confirms my former observations and enables me to add one more factor which I believe is of great importance in the production of low pressure. I refer to the altered function of the diaphragm and the accompanying splanchnic congestion and relative arterial anemia.[5]

That displacement and lessened motion of the diaphragm produce the above conditions has been pointed out by several observers during the past few years, notably by Keith, Wenckebach, and Hess. That the motion of the diaphragm is altered in tuberculosis was shown by Williams by means of the fluoroscope in 1897. The same thing was observed by Litten in observing in

this disease the alteration of the sign which bears his name. Krönig also recognizes this fact in another way by showing that the motion of the lower border of the lung is diminished when pulmonary tuberculosis is present, even though the lesion is small. Further evidence is afforded by the fact which I have emphasized in a recent paper,[6] viz., that the entire side of the chest lags even in the presence of slight apical involvement.

That this altered function of the diaphragm produces low arterial tension is self-evident, for through it the blood is allowed to accumulate in the veins, particularly the splanchnic, owing to the fact that the suction action upon the veins which is produced normally by the contraction of the diaphragm is lessened. It is well known that the splanchnics are capable of holding nearly all the blood of the body. If the splanchnics contain more than their normal amount of blood it is further self-evident that the arterial system must suffer a deficiency, with resulting low tension. I formerly pointed out that this condition probably affords additional explanation of the oft-observed fact that the tuberculous patient is pale and looks anemic when blood-counts show little, if any, anemia. The patient is caused to appear pale by the deficiency of blood in the arteries.

It might be of interest in this connection to discuss the causes of this altered function of the diaphragm. I have given this subject considerable attention in other papers and will, therefore, simply mention my own theory here, viz., that it is a part of the general scheme of protection by lessened motion which has so long been recognized in the presence of abdominal lesions, and that its cause is the same as that which produces the spasm of the muscles of the neck and chest under the same conditions—a reflex stimulation —the impulse passing from the inflamed lung to the cord, there exciting the adjacent cells of the segment and sending out stimuli to the diaphragm through the motor fibers which take their origin from the contiguous cells, causing it to assume a condition of tonic contraction or spasm.

Thus, we see that two of the factors which cause low tension in tuberculosis, the toxins and the altered function of the diaphragm, are present very early in the disease. To be sure, they become more active as the disease progresses, for as it advances the toxins increase, and as destruction of tissue goes on the action of the diaphragm is interfered with more seriously and its position in the body becomes greatly altered. Added to these factors, we also have the loss of power on the part of the heart muscle and the weakness due to general wasting. I have seen under these conditions falls in blood-pressure of from 30 to even 50 mm. Hg.

On the other hand, there are factors which are attempting to maintain pressure. Early in the disease there is an increased number of heart beats, and then an hypertrophy of the right ventricle occurs. As the disease progresses and the pressure in the lungs becomes greater, the muscular strength of the right ventricle increases,—a condition which is maintained as long as the muscle is able to overcome the added pressure.

After the disease has existed for a period of time, and the toxins have continued to circulate in the blood, the arterial walls become irritated and

thickened, just as they do under the influence of other toxins. In a study of 162 patients,[4] summarized in the following table, the condition of the radials was noted—whether palpable or non-palpable; the patients being divided into three classes: Those ill less than one year; more than one, but less than two, years; and more than two years:—

	Duration of the disease.		
Condition of radials.	Less than 1 year.	1 to 2 years.	More than 2 years.
Palpable	14	20	60
Non-palpable	14	21	33

There were 28 in Class I, with 14 palpable and 14 non-palpable; 41 in Class II, with 20 palpable and 21 non-palpable; 93 in Class III, with 60 palpable and 33 non-palpable. Thus, the interesting fact is brought out that two-thirds of those who had had clinical symptoms for more than two years had thickened arteries.

I have frequently found this thickened condition of the arteries in young people. One case, which I previously reported, that of a child of 11 years with clinical symptoms of two years' duration, showed markedly thickened arteries, and I have frequently found it in patients of 18 and 20 years.

To summarize:—

1. Low blood-pressure in tuberculosis is favored by the action of the toxins, the disturbed action of the diaphragm, and particularly, as the disease becomes advanced, by the weakness of the heart muscle and the general wasting.

2. High blood-pressure is favored by the increase in the frequency of the heart beats, the hypertrophy of the heart, and the thickening of the arterial walls.

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THE GENERAL TREATMENT OF HIGH BLOOD-PRESSURE.

By SPENCER L. DAWES,

ALBANY, N. Y.

The general treatment of high blood-pressure would naturally include the treatment by manual methods, regulated movements, and neutral immersion baths, by the means of electricity, and by sodium nitrite; but as papers on each of these particular methods appear in the Symposium and will presumably discuss the methods in detail, they will not be considered under this head. General treatment may be divided into: (1) prophylactic, (2) curative, and (3) symptomatic.

(1) Prophylactic Treatment.

A regulation of the habits of the individual as to *diet, exercise* and *excretion* constitutes the prophylactic measures indicated. Many authorities have arrived at the conclusion that while regulation of the component parts of the daily ration is of value, a far more important factor is in the limitation of the amount of food consumed. For certainly we must all agree that the best preserved, the most healthy, as well as the least senile of our patients, are those who are temperate in their habits of eating and drinking. Nevertheless it is a fact that a non-nitrogenous diet, with a preponderance of fruits and vegetables, is desirable; while a certain limited number of observers prohibit milk, eggs, cheese, and other articles of diet which are rich in lime salts, and others are insistent that the limitations of the intake of proteins is a factor which should be considered of importance.

Modern, rational, and, above all, systematic *exercise* will do more to prevent sclerosis of the arteries, and its accompanying hypertension, even than a regulation of the diet. In addition to this, most active American business men should obtain at intervals, certainly once each year, the relaxation attendant upon a sea-voyage or a period in the actual country, away from the excitement of business and society. The digestive apparatus should be kept in the best possible condition and constipation avoided, or, if the latter be present, overcome rather by a regulation of the diet than the administration of drugs.

(2) Curative Treatment.

Here we should pay our first attention to causation, such as gout, syphilis, the excessive use of alcohol, and overindulgence of all kinds; for, after all, we must admit that high blood-pressure is rather a symptom than a disease.

By far the most popular of all drugs used with the idea of cure is *iodine* in some form, given oftentimes to the point of toleration. While potassium iodide is probably most frequently used in this country, the greater number of

the French and German clinicians prefer sodium iodide, believing it to be better borne by the digestive tract; and, latterly, many so-called organic preparations of iodine have been introduced and highly recommended by the pharmaceutical houses which are sponsors for their birth.

Whichever of the salts of iodine is used, however, it is usually given in the form of a saturated solution, starting with 2 drops (which, of course, represent about 2 grains of the drug) three times each day, and each day the size of the individual dose is increased by 1 drop until 15 drops are reached, provided the stomach does not rebel. This dosage is then continued with occasional intervals of omission, a week or so at a time, for several years.

Balfour's method in the treatment of aneurism with attendant high blood-pressure he states to be as follows: "So soon as the average pulse rate in recumbency is accurately ascertained, 2 grains of potassium iodide are given every eight hours, and if the pulse rate remains unchanged the dose of iodide may be increased up to 15 grains or more every eight hours, raising it by 1 grain each dose until the pulse rate begins to rise. It is only rarely that we can increase the dose beyond 10 grains without this taking place. When the pulse rate begins to rise the iodide is stopped for one or two days, and then we go back to the highest dose that did not raise the pulse rate and continue the dose."

This use of iodine is often attended by unpleasant digestive symptoms, as well as other evidences of toxemia, and its value rests more upon empirical evidence than upon accurate measurement of the blood-pressure with a manometer. Its use is almost as strongly deprecated as it is highly commended. It is most desirable, in the use of iodine, to recollect that it should not be administered during the period of digestion, because not only is it theoretically a fact that iodine and starch produce an insoluble iodide of starch, but there are the disagreeable effects of iodine upon the digestive tract, too well known to need description here.

(3) Symptomatic Treatment.

Unfortunately most of our efforts must be directed toward relief, for the majority of our patients do not come to us until a distinct arteriosclerosis is established, and, as we have already seen, it is more often than not impossible to benefit them by curative treatment.

One of the most ancient methods in the treatment of high blood-pressure, as well as the most popular, was *venesection*, abandoned because of abuses attendant upon its use. Nevertheless, in appropriate cases it often gives brilliant results. Says Wilks: "You see your patient sitting up in bed, the face calm and lips blue or purple, and the jugular veins starting out of the neck and often visibly pulsating, the heart beating quickly and perhaps a tricuspid bruit, indicating the gorged right heart and obstructed lungs; the veins in the body are full to bursting." And here, as well as in uremia, eclampsia, and certain cases of cerebral hemorrhage, emphysema, and pul-

monary engorgement, the removal of 10 to 20 ounces of blood will prove a most satisfactory remedial measure.

Results as gratifying to the physician as they are pleasing to the patient often attend upon the free use of *calomel* or the mass of mercury, followed by a brisk *saline purge*. These measures give relief not only by the withdrawal of fluid from the intestinal viscera, with a consequent lowering of arterial tension, but by the removal from the intestines of toxic material which, by its absorption into the circulation, increases the blood-pressure; to this, I am sure, each one of us can testify.

Where there is intestinal torpor, with decomposition of the animal food, the use of the lactic-acid tablets (*Bacillus bulgaricus*) may be employed with happy results, overcoming not only digestive disturbances and the accompanying borborygmus, but the secondary production of hypertension.

The promotion of free diuresis in certain types of cases where there is an inefficiency of the skin and kidneys and myocardial degeneration, with or without valvular disease, is often of great help. Here *digitalis* is of greatest value, notwithstanding the fact that primarily it increases the arterial tension, because of its effect on the heart as well as upon the secreting functions of the kidney. For the same reason *theobromine sodiosalicylate* is often helpful; and while the effects of this drug are, in the main, produced through an increased secretion by the kidneys, yet it has a direct effect upon the vasomotor center in the medulla, and thus, secondary to this, upon the blood-pressure. A combination of these two remedies has, at times, in my experience, given results which, to the patient at least, seemed almost miraculous.

For immediate effect upon hypertension, as well as for continued use over a long period, no class of drugs equals the *nitrites,* and, of these, that most frequently employed is what is generally, although improperly, spoken of as nitroglycerin. Unfortunately the effect of the nitrites is evanescent, and the appropriate dose must be repeated at frequent intervals in order to prevent the secondary rise in blood-pressure which usually follows its primary effect. The physiological effect of the nitrites is to relax the arteries through their influence on the vasomotor system, and, as is generally the case with all rapidly acting drugs, the primary effect is not only transient, but is followed by a secondary effect directly the opposite. In addition, if large doses are given over a long period (which is the best way to give these agents), we are in danger of lowering the blood-pressure to a point where the secreting function of the kidneys is unfavorably affected. For rapidity of action in extreme cases, amyl nitrite is the most efficient; but its fleeting effect, as well as its disagreeable smell, makes it undesirable for continued use. As has been noted, nitroglycerin is most in favor, but many careful observers are strong in their preference for sodium nitrite.[1] Erythrol tetranitrate has lately been much lauded, and it has the advantage of producing a more lasting effect; but it unfortunately is an exceedingly expensive drug for prolonged use, which is just what we need it for. It should be stated that the dosage of nitroglycerin,

[1] Discussed elsewhere in this symposium.

as well as the frequency of the dose, is many times greater than is commonly supposed. In this connection I cannot help but quote what Le Fevre says: "In the treatment of cardiac and renal diseases, the greatest danger, next to the abuse of digitalis, is the unjustifiable administration of the nitrites. High arterial tension is relatively a compensating condition, and it is to be treated only when it becomes excessive. The action of the nitrites is transient, and the use of large doses at frequent intervals is apt to produce increasing irritability of the cardiovascular system, and the patient is more liable to suffer from dyspneic attacks. There is also danger of the nitrites reducing the tension temporarily below the point at which the kidney secretion can be carried on." Not all cases where there is high blood-pressure demand or even admit a reduction of the tension, for as long as cardiac power compensates for obstruction in the circulation no special treatment is needed.

THE HIGH-FREQUENCY CURRENT IN THE TREATMENT OF HIGH BLOOD-PRESSURE.

By HOWARD VAN RENSSELAER, Ph.B., M.D.,

Professor of Materia Medica and Therapeutics in the Albany Medical College,

ALBANY, N. Y.

The high-frequency, high-potential form of electricity differs so materially in its effects on the human system from the older, better-known methods of electrical application, such as the static, galvanic, and faradic currents, that it seems appropriate to give first a very brief *résumé* of some of the differences and effects of this newest form of electrical energy.

In 1891 Nicola Tesla demonstrated before the American Institute of Electrical Engineers an entirely new form of electrical discharge, and gave to it the name of high frequency.

A high-frequency current is one in which the cycles, a cycle being one positive and one negative wave, exceed in number 10,000 per second.

When a very slowly interrupted medical current is applied to a muscle, it produces a sudden muscular contraction, followed by relaxation; with a little higher frequency, *i.e.*, more rapid interruption, as in the faradic current, the muscle is thrown into tonic contraction. If the ampèrage is considerable, pain is produced; but when both voltage and ampèrage are increased, not only is a single muscle, but whole groups of muscle become convulsively contracted, and, when they are still further increased, the whole body, with every muscle, both voluntary and involuntary, is thrown into tetanic spasm and life becomes extinct.

When, however, the frequency or number of interruptions becomes greater than 10,000 cycles per second, the muscles no longer appreciate the stimulus and do not contract, and pain is no longer felt. Hence this frequency is put at the lowest limit of high-frequency currents.

As used in medicine the frequency runs much higher than this low limit, the cycles usually running from 200,000 to 2,000,000 per second, and with the tremendous voltage of from 10,000 to 500,000 volts.

Both frequencies and voltages much in excess of these limits may be freely passed through the system, but when given much higher than the limits mentioned they gradually lose their therapeutic properties on the human organism.

Just what the best frequency and the most advantageous voltage are for the effects on the body has yet to be scientifically demonstrated. Different types of apparatus and different sources of energy give somewhat different voltages and frequencies, yet all those that produce energy within the limits mentioned are capable of producing physiological actions and therapeutic effects.

We all know that the ordinary street current of 40 to 60 cycles and 110 volts, if passed through a person, will almost instantly kill him. What has happened, then, to the current which has been stepped up to, say, 500,000 cycles and 100,000 volts, to change it from a tetanizing, burning, deadly current to a mild, sedative or slightly stimulating one, which passes through the body not only without harm, but often without the person being conscious that he is in the electrical circuit?

The current of electricity is analogous to a current of any other fluid, such as water, and is acted upon by such similar forces as quantity or ampèrage, pressure or voltage, and resistance. The following simile has been given to explain the common effects:—

The overflow of a lake may pass out as a placid stream, quicken over a gentle decline, rush over the resistance of rocks in a rapid or through a rapid defile, or plunge over a precipice as a waterfall; on striking the resistance of the rocky bottom it is dashed into spray. In electricity the primary cell is the lake, the unbroken stream the low voltage, galvanic current, the broken rapids with the increased pressure the faradic current, the falls the high voltage, and the spray, produced by the tearing apart of the cohesion of the solid falls by the rocks, the high-frequency, high-potential currents, or, better, vibrations. A person struck by the solid water of the high waterfall would be instantly killed, but can stand unharmed in the midst when the water is dashed into spray. A sufficient fall of unbroken water will wash away and destroy trees, plants, and soil; the gentle spray nourishes them and stimulates their growth.

Just as the large ampèrage and low voltage electrocute a man, the atomized spray of the high-frequency, high-potential vibrations nourishes the individual cells of a person, and often restores morbid functions to a condition of health.

By the great increase of frequency and voltage the physical character of the electricity is thus entirely changed. The high-frequency current can no longer drive a motor as it did; the electrolytic action is gone; ordinary insulators do not confine it; it passes through glass as readily as does sunlight; it requires no longer a closed metallic circuit; it escapes from a single pole; it is thrown out into the air as ether vibrations, and so is used in wireless telegraphy.

Effects on the Human Organism.

On the human body the properties of the high-frequency current are: it does not kill; it does not tetanize or even contract muscles; unless concentrated at a point, it does not burn; it does not cause pain, and the body seems to offer but little resistance to its passage, as is seen in the X-ray photographs. No matter where it enters the body it penetrates every organ and tissue, and, when a Geissler tube is held by another person near to the person saturated with the electricity, the escaping vibrations will light the tube, even when held, for instance, close to the shoe of the person taking the electricity.

In its passage through the body it seems to contract or modify the vibrations of individual cells everywhere, changing or stimulating abnormally

vibrating cells, bringing them back to their normal vibrations, and thus restoring their health and function, as well as stimulating healthy cells to increased action.

Its action is thus *physiological*, and the fundamental value of this form of electricity seems to lie in the power of regulating and stimulating all nutritive processes.

From a series of physiological experiments conducted on animals and human beings, d'Arsonval, the French investigator, and others have arrived at the following conclusions in regard to the action of high-frequency currents:—

1. The respirations are quickened and deepened.
2. The heart beats more easily.
3. The pressure in the arteries is reduced.
4. The internal combustion, *i.e.*, the intake of O_2 and the excretion of CO_2, is much augmented.
5. The rate of the reduction of hemoglobin is increased.
6. The leucocytes and phagocytes become more numerous.
7. The body temperature rises slightly.
8. The elimination of the urinary solids, such as uric acid, urea, phosphates, sulphates, and chlorides, is increased throughout.
9. Perspiration is readily induced, with the still further elimination of excrementitious substances.
10. Glandular action is increased.

Thus all the metabolic processes are stimulated.

Action in High Blood-pressure.

From this rapid survey of the properties of high-frequency electricity let us turn to a consideration of its action and effects in relation to our particular topic, that of high blood-pressure.

When a person is placed in the circuit of a d'Arsonval current, *i.e.*, one of high frequency, moderate voltage, and high ampèrage, the particular form of application being called *autocondensation*, the patient at first experiences no sensation. Very shortly the operator notices, and sometimes the patient is conscious of the change, that he is breathing somewhat more deeply and fully. Then a feeling of warmth appears in the wrists, the patient holding the metal electrode in his hands. This feeling of warmth gradually extends over the whole body; a gentle glow permeates his system, and if the treatment is kept up long enough, with considerable ampèrage, he breaks out into a perspiration. Occasionally he is conscious that his heart is beating a little more forcibly. These are the only sensations of which he is conscious, and all are agreeable in character.

If the blood-pressure of a person who has hypertension is taken before the electrical treatment, and again directly afterward, it will be found to have fallen. The extent of the fall in millimeters of mercury varies with different individuals, but in general the higher the tension the greater the fall, provided marked arteriosclerosis be not present.

In most of my patients, with the type of apparatus that I use, the average fall is about 10 mm. It often falls somewhat lower during the first hours, and then gradually rises during the succeeding twenty-four hours, but usually not quite so high as it was before the treatment. The first treatments may not keep it down for twenty-four hours, but each succeeding day, if the electricity is given daily, the tension remains lower for a longer time. Usually within a fortnight it stays down longer than twenty-four hours; then the treatment is given on alternate days, and so gradually the interval between treatments is lengthened to once a week, or even once a fortnight.

The sudden lowering of the blood-pressure by this current inclines one to think that it acts on the vasomotor nerves most strongly, and very likely it does; but if it acted on the nervous system alone, one would expect that as soon as the stimuli were removed the tension would quickly rebound to its former height, the underlying cause of the high pressure not being removed. Such is, however, not the case. The persistent effect induced leads us to look elsewhere for the explanation of the more permanent results that are produced.

Its action must be to modify and improve the underlying pathological processes that are causing the high blood-pressure.

The physiological effects enumerated a few moments ago, as determined by many investigators, all point clearly to the powerful action of high-frequency currents on metabolic processes. Clinically physicians who have used this current have universally found it beneficial in almost all cases of faulty metabolism and impaired elimination in which the pathological processes have not gone so far as to cause destruction of the tissues.

The paper of this series which you have listened to on "High Blood-pressure of Alimentary Autotoxic and Metabolic Origin" brought out quite clearly the importance of toxic products in producing hypertension. With this view I am strongly in accord, believing that intestinal putrefaction is the fundamental and most frequent cause of high blood-pressure in individuals past middle life, especially in those who are high livers, who are under great nervous and business strain, and who do not take a proper amount of exercise; many of these increase their tension further by interfering still more with their metabolic processes through the excessive use of alcohol, tea, coffee, and tobacco.

Hypertension due to intestinal intoxication, in my opinion, almost always precedes; it is the toxic substances absorbed from the intestines which eventually induce the renal, cardiac, and arteriosclerotic changes so frequently associated with high blood-pressure, Bright's disease not being the cause of the hypertension.

The following case is an illustration of the general effects of the high-frequency current on a person in the earliest stage of Bright's disease, before renal symptoms were demonstrated:—

I was called one evening to see a man of 56 who an hour or two before had eaten a hearty meal, and who was feeling rather dizzy and strangely in the head. His face was deeply flushed, the conjunctivæ reddened, the temporals throbbing, the pulse full, hard, and with evident high tension. The heart was very slightly hypertrophied, and

beating so forcibly that he was conscious of it. The second aortic sound was loud and ringing. His urine was normal. His general appearance suggested an impending apoplexy. He was given at once a vasodilator and a rapid cathartic. The next morning he felt pretty well again. At my office on taking his tension I found it to be 192. I suggested as treatment the high-frequency current instead of drugs. The first application brought down the tension 10 points; on succeeding days his blood-pressure gradually lowered so that in less than a fortnight it was about 170 before each application, and after the treatment about 160. At the outset, in order to test the effect of the current alone, he was given no drug, no change was made in his diet, and no mental suggestion was made as to his condition or improvement.

About a fortnight after commencing treatment he volunteered the information that he was feeling better in every respect. He is a consulting engineer, and has to compute difficult mathematical problems. He said that ordinarily he likes to do brain work, but that for some time before taking treatment work had been a great effort, and that he had difficulty in concentrating his attention for any length of time, and that he tired easily. Since taking the treatment these disagreeable symptoms had all passed away, he felt like work again, and it did not tire him as easily as before.

On another occasion he said that he could now sleep much better than previously. Before taking the treatment he had not been able to lie on his left side. He was conscious of his heart beating, and it seemed to smother him. Now he could lie in any position without discomfort.

On still another occasion he said that the treatment seemed to be making a young man of him, so far as his eyesight was concerned; on the building across the street there was a large vine, which had hitherto been simply a blur of green, but now, having taken the treatment about a month, he could distinguish the individual leaves. On being requested to test his sight in some different way, he later reported that an awning over a store that he passed every day had seemed to have alternate broad stripes of light and dark brown; now he was able to distinguish that one of the stripes was made up of several narrow stripes of different shades, which he had been unable to differentiate or appreciate before.

I then restricted his nitrogenous diet to meat once a day; he was averaging about once a week with the treatments, his tension being about 170. One day on taking it I found it to be 190; on questioning him he confessed that he had eaten freely of sausages the day before. The sudden rise of tension was clearly the result of autointoxication from faulty metabolism, or perhaps due to some toxin in the sausage itself. Whatever the toxin was, its chemical composition seemed to be in the nature of a colloid, probably a nucleoalbumin, because with daily treatments it took nearly ten days before I could get the tension permanently down to 170. Had the toxin been a crystalloid it should have been eliminated inside of forty-eight hours. His improvement has been continuous and he now feels perfectly well.

Had this patient not taken high-frequency treatments I believe that in a few months, or a few years at the most, the intestinal toxins would gradually have produced a condition of hopeless chronic Bright's disease. Of course, a patient cannot judge whether his physician has really cured him, or has arrested his tendency to a disease and is prolonging his life; but the general feeling of well-being that he experiences after taking the treatments, the improved mental and bodily efficiency that he enjoys, and the pleasure that he gets out of life, instead of being depressed by its burdens, make him content to continue his treatments.

Conclusions.

From this necessarily incomplete and rapid study of the subject, I should like to offer the following premises and deductions.

The *premises* are:—

1. The underlying cause of most cases of high blood-pressure is metabolic, the condition arising from faulty digestion of food.

2. The hypertension usually precedes renal, cardiac, and arteriosclerotic changes.

The *deductions* are:—

1. By proper treatment with high-frequency currents the general condition, and especially the metabolic processes, are improved; hence less toxic material is formed and absorbed.

2. When, with the aid of the sphygmomanometer, hypertension is recognized early, we are able to cure the initial stages of the disease, because we remove the exciting cause.

3. The actual development of Bright's disease can be prevented.

4. When renal or cardiac lesions are already present, the rapid advancement of the pathological processes can be checked and life thus prolonged.

5. In the later stages of the disease, when compensation has broken and the heart has begun to fail, the resistance that the enfeebled organ is obliged to overcome is lessened by the lowering of tension; some of the symptoms can thereby be alleviated and the patient made more comfortable.

6. By the effect of the high-frequency current in lowering arterial tension, the brittle blood-vessels are protected from the liability of rupture, and the danger of apoplexy can thus be lessened and minimized.

SODIUM NITRITE IN ARTERIAL HYPERTENSION.

By WILLIAM HENRY PORTER, M.D.,

Professor Emeritus of Pathology and General Medicine in the New York Post-Graduate Medical School and Hospital,

NEW YORK, N. Y.

No remedial agent, in my opinion, is specifically curative. All remedies act by assisting nature to accomplish that which she cannot do by the simple use of natural foods. Used in this manner, all medicinal substances, so called, become foods of a higher chemical potentiality than the normal foodstuffs. They all act in one of two ways: First, according to the common law of heat production and its direct or indirect influences upon the nervous system. Second, by their direct mechanical, irritating, or toxic properties, brought to bear upon sluggish or inactive protoplasmic masses,—masses that will not respond to the stimulating and irritating qualities of the ordinary foods. They increase or decrease oxidation reduction, thus rapidly or more slowly displacing inactive and pathological masses of protoplasm, and ultimately producing in these masses that which is new and perfectly histological in its construction, later followed, in turn, by normal and perfect physiological activity. In this manner we can take out, as it were, a liver, or kidney, or any organ in the body and replace it by a new one. This is especially true from a physiological standard.

In attempting to elucidate the therapeutic value of sodium nitrite, or any other drug, the above facts must always be kept fully in mind. We must know the etiological factors that we are trying to remove. We must be fully cognizant of the methods by which the pathological changes are wrought. With these facts at our command we can select our remedial agents with scientific accuracy, using them to remove etiological factors, to allay symptoms, or to change directly or indirectly the metabolic processes of the body from the abnormal to the normal.

Some remedies act directly, others indirectly. Sodium nitrite should be classed with those that act indirectly, for it in no sense tends to remove directly the causes of hypertension in the vascular system. It in no measure directly arrests the progressive hardening and inelasticity of the vascular walls which is one of the inevitable results of advancing years. It will not, directly, arrest the hyaline transformation and rigidity of the vascular system resulting from syphilis. Nor does it, directly or indirectly, remove the putrefactive fermentations that are so common in the intestinal tract; fermentations which produce a host of toxins; toxins which when introduced into the blood are among the most frequent and positive causative factors for the innumerable cases of hyper- and sub- tension that we are called upon to treat.

It is in the pure hypertensions, before profound pathological changes have taken place in the vascular walls, that sodium nitrite is most valuable. In fact, it is in the management of this class of cases, which is becoming larger and larger day by day in this strenuous age, that we have our largest opportunities to display to the fullest extent the value of scientific medication.

We now know exactly what can be accomplished with sodium nitrite. The exact *modus operandi* by which it produces a dilatation of the overtense vascular system is not quite so clear. Most writers simply state that it acts like all the rest of the nitrites. This, however, gives very little information as to how it acts.

It is quite probable that, in the presence of water and hydrochloric acid in the stomach, sodium nitrite is decomposed, and that its decomposition products, NO_2 and NO, are disengaged in the form of brown vapors, which are irritants and strong oxidizers. This decomposition is known to occur outside the body,[1] and unquestionably does occur in the cavity of the stomach. These vapors ultimately produce an impression upon the centripetal nerve-endings in the mucous membrane of the stomach, which impulse is carried to the vasomotor center, and by the centrifugal nerves conveyed from the center to the vascular walls, thereby causing expansion of the vessels. This effect may be due either to inhibition of the vasoconstrictors or to stimulation of the vasodilators. The slow decomposition of sodium nitrite as compared with amyl nitrite and nitroglycerin makes it far more valuable when a continuous effect is desired.

That sodium nitrite exerts a continuous effect has been determined both experimentally[2] and clinically.

It is well known that nutritive interchange and the absorption of oxygen are dependent upon an automatic expansion and contraction of the ultimate arterioles and a regulation of the flow of blood through the arterial capillaries, in accord with the working and resting periods of the protoplasmic masses. It is also well known that the nutritive interchange occurs only while the blood is passing through the arterial capillaries. It naturally follows, therefore, that if these capillaries are continuously contracted or expanded nutritive interchange will fall below the normal standard, and that undue contraction is far more damaging than overexpansion. Overcontraction has been known to cut off the nutritive supply to the tissues to such an extent[3] that death has resulted in perfectly healthy subjects in from ten to fourteen days. Necropsies made on these subjects demonstrated that they were normal, save for the undue contraction of the arterial and capillary system. Hence the greater necessity to modify this hypertension from a purely nutritive standpoint; for without a good and well-distributed nutritive supply, pathological conditions cannot be removed nor physiological conditions re-established.

For the above reasons sodium nitrite is of exceedingly great value, before the vascular system has become too profoundly involved to be readily influenced,

[1] Richter's "Inorganic Chemistry," 4th American edition, pp. 206, 296.

[2] Archiv f. exper. Pathol. und Pharmakol., xiii, p. 138.

[3] Deutsche militärärztliche Zeitschrift, 1876.

because of its power to expand the unduly contracted arterioles. It is more valuable than the other nitrites, because its action is slower and more continuous. Its failure to accomplish the result desired is usually due to its employment in unsuitable cases. The dose is from 1 grain up, given at frequent intervals until the arteries soften.

If sodium nitrite is used in the right cases, given continuously and in sufficiently large doses, the effects are all that can be desired. The distressing symptom dyspnea, which is nature's method of indicating tissue starvation, is completely relieved, in a manner which at times is almost magic. Oxidation reduction is greatly augmented, as evidenced by the changes for the better in the catabolic products found in the urine. Thus, by the drug's action we have relieved a most distressing symptom,—we have in so far as the vascular system is concerned augmented oxidation and assimilation. Now, if at the same time, by other measures, the etiological factors are removed, the diet and digestion rendered perfect, the metabolic processes of the body can be, and often are, changed from an absolutely pathological state to one that is perfectly normal. From a purely histological standpoint we may not effect an absolute cure, but from the physiological we can.

If sodium nitrite is used when the contraction of the arterial system occurs in association with an enfeebled cardiac muscle, in which case the apparent hypertension is nature's method of augmenting the volume of blood supplied to the arterial capillaries, its use can only do harm. The same is true of the condition of engorgement of the general venous system in which, by overcontraction or hypertension of the arterial system, nature is trying to lift a greater bulk of blood back from the venous to the arterial arcade than she otherwise could, so that the blood may again be of nutritive value.

In conclusion I may state that, in my opinion, which is based upon years of experience with this drug, sodium nitrite is a very valuable remedy.

It is the misuse of sodium nitrite that has caused so many to doubt its efficacy. If it is used when and where it can assist nature, we have no more certain and reliable remedy in our whole materia medica.

Dr. Oliver T. Osborne, of New Haven, Conn., said it seemed to him that we should look at the condition as that simply of old age—normal old age, if the individual did not die by accident. What was it, then, which made the symptoms of old age arrive too soon? He was confident that this was due to diminished action on the part of the thyroid. It was interesting to him to note that the only thing which was of service in the presence of the phenomena of advancing age, when the thyroid grew less powerful and the suprarenals became stimulated, was iodine, and therefore he believed that stimulation of the thyroid was one thing that would do good. For this purpose large doses of thyroid were not required. Now, how much could we inhibit the degenerative changes? We had long known that too much meat, caffeine, alcohol, etc., were injurious. If the patient were nervous and subject to psychic disturbances, the great desideratum was rest. It did not matter whether he soaked in a warm bath or was given massage: what he needed was rest. Of the iodides, he preferred sodium iodide. It was less irritating than the potassium salt, and it was difficult to understand why the latter was so persistently adhered to in this country. As to the nitrites, we did get a continuous action from them unless actual Bright's disease were present. There were times when it was not proper to lower the blood-pressure, and therefore we could not make any fixed rules in this regard. Baking had not been mentioned, but he believed it one of the best measures at our command. However, each clinician had his own pet plan the object of which was to lower the blood-pressure.

Dr. R. D. Rudolf, of Toronto, said that, of course, the increased blood-pressure was merely a symptom, not the disease, and in many instances a rise in the pressure was of a compensatory character. As an illustration of this he would mention a case in which, with a blood-pressure of only 130, the patient had edema, an enlarged liver, and a broken-down compensation. Under appropriate treatment with digitalis, while the blood-pressure went up to 260, his liver became reduced to its normal size, compensation was restored, and he felt much better. From cases like this, therefore, we should remember that high blood-pressure was merely a symptom. Personally, he believed that gentle exercise was of material service. Its first effect was to raise the pressure, but afterward there was a gradual fall.

Dr. A. Ernest Gallant, of New York, said there was one remedy for hypertension which had been conspicuously avoided, namely, water. He had not had much experience with the scientific determination of the blood-pressure, but he had found, practically, that when "rest-cure" patients were confined in bed on an exclusive water diet, imbibing a gallon of water per day, and wholly deprived of food for ten days, arterial hypertension diminished, the pulse became slower, and its character markedly improved from day to day.

Dr. Charles E. de M. Sajous, of Philadelphia, said that Dr. Osborne had stated that in old age the adrenals hypersecreted. He thought it preferable to say that they did so only relatively to the (likewise diminished) secretory activity of the thyroid. Not only were both the thyroid and adrenals known to produce less of their secretions in advanced age, but this could be graphically shown by injecting the venous channels with colored wax. The finer radicles or tufts of the latter grew steadily fewer as age advanced, until in old age they became quite comparable to those of an old tree divested of its finer branches and foliage. But it often happened that the functional degeneration of the thyroid was more rapid than that of the adrenals; when such happened to be the case the persistent rise of blood-pressure sometimes witnessed in

old age or even past middle life was directly attributable to the adrenals. In reference to Dr. Pottenger's observation of low blood-pressure in certain cases of tuberculosis, Dr. Sajous stated that in this disease the morbid process frequently invaded the adrenals, which were then found to be the seat of one or more areas of cheesy degeneration. The secretory elements of the organs being correspondingly compromised and the volume of their secretion reduced, the blood-pressure was simultaneously lowered. In these cases it was his practice to give adrenal and also pituitary body. These agents did not cure, but they helped to sustain tissue oxidation and the contractile efficiency of the cardiovascular system.

Dr. W. A. Campbell, Colorado Springs, Col., said that the profession at sea level or low altitudes had much difficulty in arriving at a definite understanding as to what the standard blood-pressure was for man, owing to the many conditions within and without the body influencing the blood-pressure. The experience of investigators at low altitudes had been duplicated by those at high altitudes, with the additional difficulty of want of stability in residence. In the past we had been told, in turn, that the arterial pressure or tension was raised, that it was diminished, and that it remained unaffected in high altitudes. From thoroughly reliable recent experiments by Drs. Gardner and Hoagland, Prof. Schneider, and Dr. Hedbloom, it was now pretty positively known that at Colorado Springs, with an altitude of 6000 feet, the blood-pressure was 5 mm. lower than at sea level, and on Pike's Peak, altitude 14,147 feet, it was 5 to 7 mm. lower than at Colorado Springs.

Dr. Francis M. Pottenger, of Los Angeles, Cal., said he was glad to learn that the high-altitude men were beginning to recognize that altitude lowered blood-pressure. The best work that had been done along this line showed that this was actually the case; yet, altitude enthusiasts repeatedly asserted that one of the most valuable effects of high altitude was that of raising the blood-pressure.

Dr. Alfred C. Croftan, of Chicago, said that he took issue with Dr. Dawes in regard to the action of small doses of digitalis. It was a well-known fact that small doses of digitalis, that is, a drop or two of a fresh tincture, were capable of reducing the blood-pressure in cases of intestinal self-intoxication. This fact had been first established by Grodel, and through a series of experiments performed by Brandenburg. It had been found that a watery extract of feces injected into a rabbit under certain precautions could produce a rise of blood-pressure. If, now, two rabbits were injected in this way, the one, however, being placed under the influence of small doses of digitalis, then it would be found that a pressor effect was not produced in the digitalis rabbit; showing that the digitalis exercised to some extent a regulatory effect upon the blood-pressure mechanism, rendering the circulatory apparatus less susceptible to the intoxicating effect of the fecal extract.

The speaker claimed never to have seen any marked effects upon blood-pressure from the use of iodides, although the latter were generally advocated in the medical literature. At the International Medical Congress in Wiesbaden, several years ago, this question had been fully discussed. The chief claim for the iodides was that they reduced the friction of the blood, that is, its viscosity. Experimental work, however, performed with accurate methods, negatived this postulate. As far as the use of large quantities of water in the reduction of hypertension was concerned, he expressed himself as very much more in favor of drink restriction, with the accompanying restriction of sodium chloride. Occasionally in cases of profound intoxication it might be precarious to reduce the liquid intake below a certain level, as the possibility of a concentration of toxic body fluids, and hence a greater toxicity of the latter, might be promoted. As a rule, however, the mechanical element of reducing the amount of labor imposed upon an already overtaxed cardiovascular apparatus was the more important factor.

THE PROPER TREATMENT OF DIABETES MELLITUS AND ITS CURE BY DIET.

By LOUIS KOLIPINSKI, M.D.,

WASHINGTON, D. C.

"Après quarante ans de pratique, je n'ai pas encore trouvé à ma clinique un seul diabétique qui ne m'ait trompé, ou n'ait tenté de le faire. Aussi, ai-je peu d'illusions sur la stricte observance des régimes qu'on prétend leur imposer. Il en est tout autrement avec les sujets appartenant à une autre condition sociale, et qui, dans une maison de santé, se soumettent volontiers à certaines obligations parfois pénibles mais dont ils comprennent l'utilité."

R. LÉPINE, "Le Diabète Sucré."

UPON the mind of the practitioner who has attempted to read the immense medical literature of diabetes mellitus of the past one hundred and fourteen years a throng of startling thoughts force themselves. His wonder is intensified when he muses upon the nature of the disease, its symptoms, its terminations, the mystery of its origin and cause, and the disappointing results of the ordinary and extraordinary efforts at treatment. The whole subject, however approached or surveyed, is confusing, contradictory, and perplexing. On every side one great riddle presents itself. In its development, its pathology, its chemistry, and the organs involved or at fault, the disease has baffled and confused the investigators. Cure and recovery are uncertain, misunderstood, and even relinquished from dread of the inveteracy of the malady.

The practical end to such a train of reflections is the direct query: Can essential diabetes mellitus in man be cured so that health is completely restored and life will run its natural course to its termination in old age?

From the chaotic heap of theory, experiment, observation, and contradiction composing the medical history of the disease the truth can nevertheless be extricated, and the answer to the question propounded is that diabetes mellitus in man, free as yet from dangerous complications, is easily curable, in proportion to the accuracy and persistency of the treatment, as well as the honesty and truthfulness of the patient.

The fact of greatest significance in the treatment of diabetes mellitus is that it is curable by diet. The fortunate and consistent reasoning of Dr. John Rollo which led to this discovery, successfully applied by him, has not, however, been rightly valued and fully estimated by succeeding practitioners. That diabetes mellitus is curable by diet does not state the principle completely or correctly. Rather must it be said that diet alone is the cure for the disease, that by any other means this is an impossibility, and that the use of any medicine, drug, organ extract, ferment, or enzyme is worthless and therefore injurious.

Before proceeding to a description of the method of diet which has proven accurate and successful in practice, the following working theory of the disease is submitted as one that is simple, consistent, and in harmony with our knowledge of the history of the malady in its progression from the antecedents of a patient until his end:—

Gout and diabetes mellitus are allied and analogous in many respects. Both spring from obesity. The obesity of gout arises from the daily use of alcoholic drink, together with the eating of much food, be the life led that of the wealthy epicure or that characterized by enormous beer drinking in the common man. Alcohol is always, lead occasionally, the direct cause of gout,—primarily of the transmitted form. Gout, obesity, and diabetes mellitus are hereditary diseases.

Diabetes mellitus is not caused by strong drink, but by overeating to a degree of marked robustness in the laborer or of overfatness in the sedentary. Every diabetic has a previous habit of obesity or of excessive eating. Often there is a fondness for particular foods or dishes with an excess of vegetable carbohydrates. Confirmation of this statement can be found with the family of the subject or with his habitual companions; self-observation is always inaccurate.

From these elementary statements there follows: (1) that gout precedes diabetes mellitus, but that the reverse is not true; (2) that diabetes mellitus is more common among people who eat much, but refrain more or less from alcohol,—a fact noted in the Hebrew race; (3) that diabetes mellitus is found in children who overeat, but gout never; (4) that diabetes is much more common in women than is gout because they are less given to drink than men.

The lesions of gout result from the uric acid in the blood and tissues which finds no natural excretory channel, or from the agent of its oxidation or reduction.

The lesions of diabetes mellitus result from a permanent increase of glucose in the blood and its persistent discharge with the urine. The essential cause of this is the destruction, more or less permanently and completely, of the glycogen-forming function of the liver. All ingested carbohydrates appear as sugar in the blood and in the urinary excretion. It is the persistent excessive consumption of a vegetable or mixed diet which in most cases first leads to obesity,—markedly so in the middle-aged. It is in the less resistant, less hardy and enduring that the conversion of sugar into glycogen in the liver-cells is arrested for all time.

Whether this be due to a permanent vasomotor paralysis in the liver, like that which temporarily results from the piqûre experiment of C. Bernard, in the medulla oblongata, or whether it be a glandular or cellular atrophy, or the absence of a ferment engendered in liver or pancreas or some other agent of internal secretion, the diabetic subject is permanently bereft of the power of extracting sustenance from sugar and starch. He must henceforth abandon the proverbial staff of life—bread—or death will be the consequence.

Granting, therefore, that the liver's glycogen-forming power is destroyed by overuse, that this internal food is no longer stored in the liver-cells, and

that through the lymphatic and vascular systems glucose circulates unchanged and unconverted, it is plain that the search for any curative medicinal agent is vain. The continued eating of sugar and starch and the continued glycosuria will hasten to its conclusion a disease always in its nature fatal: acute and rapid in the young, slow and chronic in the old. The youth is doomed by a glycosuria which nothing can retard or suppress. No diet will cause the sugar to disappear; the disease is in the grave or severe form. In the old subject glycosuria may vanish or be lessened in quantity by diet; the disease is in the mild form.

If, however, man can live and grow on a diet containing but very little of carbohydrates or none at all, no evidences of the continued existence of the disease need appear. No sensation or manifestation of ill health will be felt or perceived, and the subject formerly affected will live on in continued good health; for it is admitted by everyone who has studied diabetes that the main source of glycosuria is the food consumed, its amount, and its kind.

That this can be done and is even easily possible will be shown, and the proof will be held to be that such a diet is capable of permanently removing all traces of morbid sugar from blood and secretion, of overcoming all minor non-fatal lesions of diabetes, and of restoring to the body its standard weight and, if desired, an excess thereof.

Having determined in the ordinary case of diabetes mellitus the specific gravity of the urine, the absence of albumin, the presence or absence of acetone and of diacetic and β-oxybutyric acids, and the presence of grape-sugar, by a copper or bismuth test, verified by fermentation of the liquid, the chemical reaction is repeated as a demonstration before the patient, unless the latter be a small child. The chemical manipulation by which grape-sugar is identified is explained. Furthermore, the patient is told that the disease is easily curable by diet, not by drugs, that so long as no sugar is found in the urine he is well, that the finding of sugar means transgression in diet or error in the preparation of food, and that the continued presence of sugar in large or small amount, as proven by the tests employed, will render the disease a fatal one. It is explained that sugar will no longer be found after the third or fourth day of antidiabetic diet. The patient is furnished with a written or printed copy of the latter, as follows:—

Breakfast.—Artificial milk, eggs, ham or bacon and eggs, beefsteak, lamb, mutton, fish (fresh, salted, or smoked), raw tomato. A small cup of coffee or tea with cream.

Dinner.—Artificial milk, clear broth, raw tomato and lettuce with mayonnaise dressing, onion, cucumber, pickles. Any kind of meat, fish, game and fowl, sausage, tongue, brain, sweetbread. Any kind of cheese.

Supper.—Artificial milk, fish or eggs, cold meat, cheese, schmierkaese or curds; a glass of cream, tea, or coffee with cream.

At Bedtime, if Desired.—Artificial milk or a glass of cream.

After three or four months the following vegetables and fruits may be tried at the same time the urine is tested for glucose (should it reappear the offending food is eliminated): Asparagus, cauliflower, boiled onion, cress,

spinach, endive, cabbage, sauerkraut, green beans, turnip, radish, kohlrabi, apples, cherries (Strümpell).

The artificial milk referred to consists of a modified formula of a series of liquid foods imitating milk chemically, devised by the writer and described in the *Medical News,* New York, December 21, 1901. It is prepared as follows:—

1 broken raw egg.
2 teaspoonfuls of malt extract.
4 teaspoonfuls of olive oil.

Beat up in a bowl with a spoon or egg-beater for five minutes. Add gradually while stirring 1 pint of drinking-water. Season to the patient's taste with table salt. In hot weather add crushed ice.

Varied and oft-repeated experience has proven that this dietary is amply sufficient to sustain and nourish the body to the point of inducing an increase of weight approaching obesity, *i.e.,* it is food more than enough for life, comfort, and health.

No medicinal agent is used in the treatment except the following saline purgative, which is administered when the patient is constipated, has hemorrhoids, is obese, or where it is desired to reduce the weight to normal. This combination is most valuable and efficient for relieving an engorged portal circulation. Its action is not depressant, like that of magnesium sulphate or the purgative mineral waters containing it. It acts in thirty to forty-five minutes, and with great certainty:—

℞ Sodium phosphate,
Sodium sulphate ..... of each ʒiv.
Dissolve with shaking in a quart bottleful of cold water.

The solution is a saturated one; a small amount of the salts remains undissolved. The dose is a wineglassful in a tumbler of cold water fifteen or twenty minutes before breakfast or supper. As the indications vary, it may be taken once or twice a day or two or three times a week, for an indefinite period.

Another similar formula in imitation of the constituents of Carlsbad water, but better than this renowned mineral spring, is the subjoined:—

℞ Sodium chloride ..... ʒiij.
Sodium bicarbonate ..... ʒiv.
Sodium sulphate ..... ʒiiiss.
Sodium phosphate ..... ʒiv.

It is dissolved in the same manner and in the same amount of water as the first, and is taken similarly in time and quantity. Its action is somewhat milder, its taste more pleasant, and it is gently antacid.

The diet above described, when partaken of for three or four days, invariably brings the specific gravity of diabetic urine to normal or subnormal, and not a trace of glucose can be detected by our customary tests. With this normal urine the diabetic returns to a state of health, the thirst, hunger, and excessive urination disappearing in a few days. The languor, weakness, and aching of the muscles are no longer perceived. The less grave lesions of

the skin—eczema, pruritus vulvæ, furunculosis, carbuncle or phlegmon, and the peripheral gangrene of fingers or toes—heal spontaneously, and acetone, diacetic acid, and β-oxybutyric acid, which may have been found originally, are no longer present in the urine. An incipient diabetic cataract may clear up. The scorbutic appearance of the gums disappears, and loosening of the teeth is relieved. The diabetes is thus cured, as it were, by crisis, and remains so in proportion to the faithful observance of the regimen prescribed. Those diseases which always end life in the diabetic, viz., pulmonary tuberculosis, pulmonary gangrene, chronic nephritis, extensive gangrene of the extremities, or multiple carbuncle, both with profound sepsis and persistent acidosis or diabetic coma, cannot, of course, be cured in this way. But as surely as these complications are always fatal in their progression, so are they always absent in the diabetic whose urine is kept permanently at normal.

With the method described the disappearance of the sugar is absolute and does not depend on how recent or how old the case, how mild the symptoms or how severe, and how little or much glucose is found in the urine. The urinary sugar of diabetes mellitus comes only from carbohydrate food, and vanishes when none is taken and a true antidiabetic diet inaugurated. Glucose in the essential diabetes of man does not come from fat or proteid, whatever may be the condition found in experimental glycosuria, such as is produced by extirpation of the pancreas or resection of the duodenum.

In practice we find, however, ambulatory and unrestrained diabetics in whom a diet as efficient as the one described does not entirely eliminate the sugar from the urine, the glucose persisting with a fixedness that baffles and discourages the inexperienced practitioner. Such cases are those of the "severe type," as first classified by Seegen.[1]

This most unfortunate appellation, repeated everywhere by medical writers, cannot fail to cause much harm in the treatment of diabetes. In these unfortunates sugar still appears in the urine, though the diet be strictly and wholly albuminous. The liver is unable to make good all of this saccharine waste. The muscle glycogen and that in all other parts of the body is called upon. The nitrogenous and albuminous foods and the fats are likewise supposed to be turned into sugar and all of these sources do not suffice to stop this consumption of the body or mitigate the intensity of the disease.

A diabetic at almost any time or state of his malady when following the diet described begins in seventy-two hours to pass urine entirely free of sugar, which so continues as long as the food is the same. Therefore in each and every instance where glycosuria persists, it means that the diet has not been interpreted correctly and other food ingested in addition, *e.g.*, gluten bread, ice-cream, milk, or other harmful things, eaten in the belief that they are of no significance or else (which in practice is found oftener to be the case) by willful and flagrant disregard of the instructions on the part of the patient. This leads to the unexpected discovery that, although the diabetic solemnly declares that the diet was followed as given, nothing else what-

[1] Der Diabetes Mellitus, 1870.

ever was partaken of by him as food or drink, and that he is innocent of deception or prevarication, yet he is guilty of both. That anger or haste may not destroy the practitioner's intent to help the sick it is wise to have patience and forbearance; later, by inquiry in the patient's family or of the housekeeper, there will be discovered the obnoxious food or drink responsible for the ill success of treatment. Often the prime mover and instigator of this duplicity on the part of the patient is some member of the family or a relative or friend who either does not favor the principles of proper treatment, is ignorant of the gravity of the disease, favors indulgence in eating to the diabetic, or believes the diet harsh or cruel. To some such influence the victim's integrity yields, and the disease persists as before.

Some diabetics, when their duplicity is detected and exposed, will confess great fondness for eating; others, that the diet is too rigid; others, that the eating of anything strongly desired cannot be followed by harmful consequences, or, lastly, that surely it is against reason and all natural right that bread should be interdicted forever,—not the giving up of fire and water, but of bread, the mainstay of mortal life. This primitive form of daily food is so ingrown into our nature and instinct, is so closely associated with our ideas of aid in hunger and starvation, of charity and alms, that to view it as the prime cause of a deadly intoxication is impossible for the laity to conceive or understand. Yet in this extraordinary malady it must be given up for an indefinite time, or all attempts at cure will be futile.

When at the diabetic's second consultation the urine is found normal, and this fact has been demonstrated to him by the tests already used at the former interview, he is instructed to return every week or two for further supervision. The sugar reaction never reappears, the symptoms are lost, the health returns, and he is at liberty to pursue his customary work or occupation. With a patient who is faithful and adheres rigidly to the requirements a monthly analysis for glucose is sufficient. After six months or a year slight additions of carbohydrates to the diet may be made if the patient so desires. Frequent examinations must be made in order that the physician may convince himself that such experiments are not harmful in causing a return of the disease. In fact, should the diabetic elect to continue the regimen that has cured him and beyond doubt saved his life from a deadly disease, he should be induced and encouraged by every available argument to follow such a determination.

It is of great importance to guard a cured case from the former habit of overeating and obesity. The diet already described is prone to lead to the latter condition, owing to liberal consumption of the artificial milk. Should the body weight begin to rise above normal or the patient present any evidence of dyspnea or cardiac insufficiency, the daily quantity of the emulsion taken may be reduced, or else a daily dose of the saline purgative already advised employed in order to bring the weight, in the course of a few months, to its normal standard.

Of the use of tobacco and liquor in diabetics, it may be said that neither is harmful and that neither can aggravate the malady. They must, however,

be used sparingly and with proper discrimination. Two cigars per day or two or three pipes of smoking tobacco, an occasional glass of whisky, sherry, or of other wine, not sweet, may be allowed, but not commended to the patient. Champagne and malt liquors, particularly lager beer, will prolong the glycosuria indefinitely.

Treatment of Symptoms, Minor Lesions, and Complications.

The treatment of the symptoms, minor lesions, and serious complications of this mysterious malady, diabetes, requires brief and practical discussion.

The symptoms most generally complained of—languor, weakness, thirst, hunger, and excessive urination by day and night—vanish in a few days with the appearance of normal urine.

The eczema, genital pruritus, and furunculosis disappear in a week or so.

It is a characteristic complaint of grave cases to be tired to death, or so tired as to wish for death, and this languor the patient does not observe to disappear as quickly as the polydipsia and polyuria. The use of drugs to relieve these acute subjective symptoms, and particularly the hunger and thirst, is most injudicious, and the praise given to the use of opium by writers of authority is to be deplored.

The *carbuncle* of diabetes mellitus, of all carbuncles, should never be operated upon by excision. It is not at all necessary, and the danger to life is very great. Diabetic coma is always imminent. Far better is it to cure this infection of the skin by means of precipitated sulphur, applied as a powder into the points of suppuration or ulceration, or used as an ointment with a cocoa-butter base (1 to 8). Equally efficacious to render a carbuncle innocuous is the constant application of a compress wet with a solution of calcium creosote.

Extensive *gangrenous phlegmons* must be incised and then thoroughly dressed with the same applications.

Diabetic cataract, when in its incipiency, may clear up under the antidiabetic diet.

Albuminuria, where faint and incipient, may likewise entirely disappear. Where it is an essential part of subacute or chronic nephritis, an attempt to cure these may be made with a diet consisting of 2 pints of cream a day, whole or diluted with water, and an abundance of curds or schmierkaese. When the albuminuria has practically disappeared, the artificial milk is added to these two foods.

Cows' milk cannot be used in treating diabetes or the succeeding nephritis. With a milk diet it is possible in the nephritis of diabetes to remove the urinary albumin entirely, as well as the dyspnea and anasarca, and very rapidly to increase the strength and weight of the patient; but soon after, the glycosuria, previously very much reduced or for a time even absent, will reappear. With this the diabetic dyscrasia returns in its full intensity. A meat diet now produces a fresh albuminuria, the sugar again receding, and

death finally results. It may occur as a result of both diseases,—gangrene of a lower limb and uremia.

Milk has been allowed as a food in diabetes by many practitioners, and has been approved as proper in the diabetic form of nephritis, but not wisely, as it is agreed that the ingestion of lactose in diabetes increases the glucose in the blood. In the abandoned skimmed-milk treatment of Donkin,[2] the singular error was committed of taking away useful food substances and allowing sugar of milk, a harmful one, to remain.

Gangrene, when superficial, heals spontaneously or with boric acid compresses or baths.

Deep or complete gangrene of a limb gives a heavy mortality after operation. In such cases the prognosis is always unfavorable unless the patient reacts to the proper diet, which alone can save the life that is in jeopardy. Gangrene, like albuminuria and all other complications, never appears where dieting has permanently rendered the urine normal.

The *pulmonary tuberculosis* of diabetes is insidious, never chronic, rapidly fatal, with deep sepsis and enormous wasting of the body. Hematemesis may be the first evidence of a disease already established. Equally as fatal as tuberculosis, and sometimes a part of it,—at other times after a croupous pneumonia,—is *pulmonary gangrene.* The antidiabetic diet always eliminates the grape-sugar in the urine, but never retards the rapid progress of either of these diseases.

True glycosuria occurring in the course of typhoid fever requires no treatment until the temperature is normal and convalescence begins. The sugar, as is known, disappears in four or five days from the onset of the fever, reappearing when the disease has run its course.

Syphilis, secondary and tertiary, should be treated as in the non-diabetic. Antisyphilitics, like all other well-known remedies, have no power to alter the state of glycemia, and lues, present or passed, or its treatment, neither aggravates nor mitigates the associated disease.

Beginning acidosis may vanish, and the acids and fat derivatives found in the urine in cases near to a fatal ending likewise be removed together with the sugar under the influence of diet; but where great weakness, drowsiness, labored breathing, and beginning stupor herald the oncoming of diabetic coma, the case is a lost one. Perhaps the discovery of a suitable antidote for acetone and diacetic and β-oxybutyric acids in the blood, or of an eliminant, will eventually lead to success, or else, by transfusion or the introduction of enough water into the stomach to dilute sufficiently the poisoned blood, better results may be obtained than those now achieved; but as yet the coma of diabetes is still the most rapidly fatal of all of the dangerous complications to which its victims are exposed.

The correct diagnosis of diabetes mellitus, essential and idiopathic, in man is easy and extremely accurate. The stage, associations, and future of the disease can all be discovered and foreseen.

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2 Lancet, London, 1869, ii, 1871, 1873.

The blood and urine must contain glucose in excess of that which is at any time transient or accidental. Subjective and objective symptoms of the activity of the disease must also exist. Without these a true diabetes cannot be present.

A glycosuria can be encountered under a great number of conditions of ill health, in the presence of injury, and as a result of the action of drugs and poisons or of an excess of carbohydrate food.

Besides grape-sugar, other sugars may be found. These are prone to lead to error in an incomplete examination. Levulose, lactose, and pentose may be the cause of mistake.

As none of these conditions constitutes true diabetes or has anything in common with it except sugar in the urine, with or without a glycemia, it may be proper to enumerate those most likely to lead to confusion, since if treatment is indicated it must necessarily be different from that here described for true diabetes.

Among these various glycosurias[3] is the alimentary form, due to excessive consumption of carbohydrate or sugar as food and to which various morbid states of the economy predispose, *e.g.*, fevers, chronic disease of the pancreas, brain tumor, hysteria, melancholia, traumatic neuroses, simple trauma, Basedow's disease, thyroid gland medication, delirium tremens of alcoholism, lead colic, carbon monoxide poisoning, obesity, pregnancy, and the use of diuretics.

Glycosurias are also met with in disease and injury of the cerebrospinal system, in surgical traumatism, in chronic disease, and in many intoxications and poisonings.

Thus, glycosuria may be present in the case of lesions of the cerebral hemispheres, in brain trauma, brain commotion, and injury of the floor of the fourth ventricle, and in excitation of a sensory nerve, as in sciatica, traumatic neuroses, and fractures.

In the insane, in tetanus and hydrophobia, and in poisoning with phlorhizin, chromic acid and chromates, uranium salts or cantharidin (these last noted in animal experiments), glycosuria may also occur.

Toxic glycosuria with hyperglycemia, the type of which is that produced by epinephrin, may result from hydrocyanic acid, chloral hydrate, chloroform and ether anesthesia, morphinism, alcoholic delirium tremens, mercury, and phosphorus.

In intermittent fevers, anthrax, diphtheria, pregnancy; after attempts at suicide by drowning; in burns of the skin; in Basedow's disease and myxedema; in intestinal worms; in cholelithiasis, glycosuria has also been observed. Alimentary glycosuria is transitory in surgical pancreatic diseases and is not common in acute pancreatic disease.

Various kinds of disease have been found to be occasionally followed by a diabetes, and have therefore been held among its causes. The diabetes in all instances is purely secondary.

The antecedent disease always has its own symptoms and features, as well as its own treatment, imperatively indicated. Though a diabetes may

[3] R. Lépine: "Le Diabète Sucré," 1909.

occur, much oftener it is not present; just as often a diabetes insipidus or a transient glycosuria is observed.

The attempt to discover the primary cause of diabetes, rendered more mysterious by animal experimentation, has resulted in the recognition of several types of the disease designated by the organ or part affected.

Among all the various causes of diabetes the following are the most prominent:—

Syphilis of the nervous system, lesions of the cerebral hemispheres with diabetes insipidus, lesions of the vagus and of the sympathetic nerves, traumatism of the head, vertebral column, and abdomen; surgical operations, depressing emotions, hepatic cirrhosis, pancreatic cirrhosis (bronzed diabetes), chronic pancreatitis from pancreatic calculus or obstruction of the duct of Wirsung by a biliary calculus or through cancer of the head of the pancreas, chronic pancreatitis resulting from syphilis or arteriosclerosis, acromegaly, Basedow's disease, and tumors of the suprarenal gland, mainly sarcoma.

In concluding, I would like again to refer to the treatment. In a number of cases of diabetes cured by means of the treatment already described, the previous duration of the malady had been from one month to twelve years. The age varied from young adult life to old age. The majority of the patients were willing and docile after the disease and its pathology had been explained to them and the change from disease to health shown in the urine by the chemical test. In these subjects, followed a sufficiently long time, retrocession was never observed while the diet was being continued. The shortest cures extend over six months, the longest three years. The diet was not found tedious or repulsive. The morbid or childish desire for bread was neither felt nor expressed. In fact, to anyone for whom life has the charm of health, family, friends, pleasure, work, or study, and who has been taught a good working theory of the cause of his disease, even this dietetic treatment has its attractions. Before, too much food was eaten; now, it is a matter of selection and choice. The results described are invariable and extremely precise, and the claim is reiterated with confidence that by this method any diabetic free of terminal disease can be speedily and permanently cured.

DISCUSSION.

Dr. Alfred C. Croftan, of Chicago, in all kindness felt obliged to take issue with a number of the statements made by the reader of the paper. First, in regard to the cure of the diabetic cases described. Dr. Croftan from his personal experience was decidedly of the opinion that a person once a diabetic was always a diabetic. While it might be a simple matter in the milder types of the disease and in symptomatic cases of glycosuria of varying origin to keep the urine sugar-free on a diet low in carbohydrates, it was certainly not an easy matter to do this, and occasionally quite impossible, in the cases of medium severity and in the very severe types of diabetes. The statement of the essayist that the only source of sugar is the carbohydrates of the food was also to be denied; for severe cases of diabetes, even though they remained for weeks and months on a carbohydrate-free diet, still continued to excrete sugar. This sugar would have to be elaborated from the patient's own tissues, and it would often be found that a reduction of the nitrogenous food led to a reduction or a disappearance of the urinary sugar; in fact, it was well established that the albumins of the food

constituted almost as important a source of urinary sugar as the carbohydrates. It was exceedingly important in the treatment of diabetes to individualize, to establish the type, the degree, and the category of diabetes or glycosuria that one was dealing with. Diabetes was only a symptom of a variety of underlying causes. Dr. Croftan then described some practical methods of determining the type and degree of diabetes and of making simple tolerance tests for various starchy foods, and fully discussed the equivalent values of the different carbohydrates in the ordinary diet. To keep a patient for an indefinite period upon a strict diabetic diet was decidedly bad practice from several points of view. In the first place it was exceedingly difficult to maintain adequate nutrition for an indefinite period on such a diet. In the second place, the psychic stimulus of appetite so essential to proper digestion was withheld. In the third place, the tendency to acidosis with resultant coma was increased. Even a normal subject after ten to twenty days of a carbohydrate-free diet would excrete acetone and its congeners in the urine, and this acetonuria could be promptly made to disappear by the administration of even small quantities of carbohydrate pabulum.

It should be recognized that in most cases of diabetes it is more important to maintain adequate nutrition, a proper body weight, and a sense of strength and well-being, than to devote all endeavors toward ridding the urine of the last traces of sugar. Most patients, being confronted with the alternative whether to live ten years with a little sugar or one without any sugar, would choose the former option. To paraphrase a noted clinician, it was much more important to know what kind of a patient the diabetes had got than what kind of a diabetes the patient had. The peculiar relation of diabetes with gout and obesity was well established. These three disorders belonged to the same class clinically, pathogenetically, and chemically, for in all three of them, broadly speaking, there was a reduction in the power of destroying the carbohydrates, the proteids, and the fats, and not, as is so commonly claimed, a tendency to an overproduction of these substances. If the normal destruction of the carbohydrates was reduced, then the carbohydrates must accumulate, and hyperglycemia and glycosuria resulted. Where the destruction of certain albumins (nucleins) was reduced, there occurred accumulation of nuclein derivatives (purins), with the manifestation of gout and the uric acid diathesis. Where the fat destruction was reduced, an accumulation of fat in the tissues took place. There were numerous combinations of these different diseases, the most notable one being the obese form of diabetes or the diabetogenous form of obesity. Here the diabetes, one might say, had been existing for a long time, but the sugar, instead of being excreted in the urine, was converted into fat and temporarily deposited in the tissues. Under the influence of a variety of impulses this process became inverted and the fat was rapidly reconverted into sugar, the latter being excreted in the urine in large amount. In these cases the diabetes rarely lasted for a long time. A great deal of fat was lost within a few months and then equilibrium seemed to become re-established. To place such patients for an indefinite period upon a carbohydrate-free diet was a very precarious matter, altogether unnecessary, and decidedly bad practice.

Dr. Charles E. de M. Sajous, of Philadelphia, said that he agreed entirely with the views expressed by Dr. Croftan. Each case of diabetes had to be studied individually, and he had yet to find five cases which he would treat in precisely the same way.

Dr. Oliver T. Osborne, of New Haven, Conn., said he agreed with Dr. Sajous. He would like to emphasize the danger of acidosis resulting from sudden reduction of the starch diet. It was proper to give the patient a little carbohydrate, for it would not do to make him manufacture sugar out of meats and fats. In operative cases he always loaded the patient up with oatmeal gruel before the operation in order that he might not die of acidosis. The condition of affairs was similar to that met with in the vomiting of pregnancy. He thought, therefore, that one should allow starch in small quantities in true diabetes.

Dr. H. Beaumont Small, of Ottawa, said that, after all, he thought the hearers of the paper might agree with Dr. Kolipinski, who seemed to have excluded from consideration the severer forms of diabetes. In this discussion no allusion had been made to gluten. The difficulty was to get a good gluten flour, as most of those on the market were frauds and delusions. He had found that the production of sugar seemed to be favored by other agencies than starch in the diet. Thus, he had under his care at the present time a diabetic patient, an organist and choir master, who on Saturdays and Sundays, when he was under a mental strain in drilling and controlling his choir boys, showed almost invariably a decided increase in his glycosuria, although no change had been made in his diet. During the rest of the week his urine was free, or comparatively free, of sugar.

Dr. Francis M. Pottenger, of Los Angeles, Cal., said he had had a number of cases of diabetes among his tuberculous patients. One of these had lost his glycosuria entirely when he had the misfortune to be struck on the head with a croquet-ball. The blow had not been a severe one, but it had affected him seriously. He had taken to bed, and, with no change in his diet, the sugar had returned. This patient had died not long afterward from pneumothorax, and maintained his sugar until the end. The points of interest were the loss of sugar as the underlying tuberculosis improved, although the patient was not on a specially restricted diet, and then the return of sugar after the slight injury.

Dr. Osborne said he believed that, next to Dr. Wiley's work in giving us pure foods, impure (starchy) gluten flours had saved more lives than any other agency.

Dr. Kolipinski, in closing, said that he had not been able to eliminate sugar from the urine under the use of gluten bread. Diabetes was undoubtedly one of the most fascinating riddles met with in medicine. The most interesting point in regard to it was the correct diagnosis. True diabetes was characterized by special symptoms, and the observation of much or little sugar in the urine he thought amounted to nothing. He had never had a case in which he could not eliminate the sugar permanently. But aside from the matter of sugar and the associated acids in the urine, it was necessary to watch the patient closely and keep a careful record of his condition, so that he might be kept up to his normal weight, or above it. He would be lost if he should continue to lose weight steadily.

MODERN METHODS OF DRUG STANDARDIZATION.

By F. E. STEWART, M.D., Ph.G.,

GERMANTOWN, PA.,

WITH THE COLLABORATION OF

A. PARKER HITCHENS, M.D.; W. F. ELGIN, M.D.; CHAS. E. VANDERKLEED, Phar.D., and P. S. PITTENGER, Phar.D.

My object in presenting this paper is to place in the hands of the American Therapeutic Society a plan for teaching drug standardization which has been employed during the past winter by myself and associates in lectures before the Philadelphia College of Pharmacy, Temple University, and the Pharmaceutical School of the Medico-Chirurgical College, and also utilized by several of us in papers read before medical and pharmaceutic societies.

The subject-matter is largely a compilation derived from many sources, both in this country and abroad. The data have been collected and classified for the convenience of teaching students, especially in pharmaceutic colleges. However, judging from the want of appreciation of the wide variation in medicinal drugs, chemicals, and preparations of the same, by the medical profession, much of the information in the paper could be advantageously used for teaching the medical students.

Any and all methods for improving the character, quality, and strength of materia-medica products and securing their uniformity may be properly considered as methods of standardization, but, in the specific sense of the term, standardization means the adoption of definite standards and conformity thereto.

The necessity for securing definitions in the character of drugs has never been fully realized. No one has questioned the necessity for preventing gross adulteration and sophistication, but consideration of standardization by which drugs are rendered instruments of precision has never been given proper consideration until very recent times.

It must be apparent to any thinking person that adulteration of drugs or their sophistication must of necessity materially influence their physiologic action and therapeutic value. Even the impurities resulting from the processes of preparing medicinal chemicals may seriously modify their therapeutic effects. Variation in active principles in medicinal plants is another factor of importance in considering the question of standardization.

In no better way can we obtain an adequate idea of the subject of modern drug standardization than by a brief review of the standardization work of the United States Pharmacopœial Convention and its Committee of Revision during the past two decades.

Long before the enactment of the national pure food and drug law of June 30, 1906, necessity for accurately defining the limits of purity permissible in official chemical substances became so apparent that the Pharmacopeial Convention of 1880, and its Committee of Revision, met the question by inserting more definite descriptions with qualitative and quantitative tests in the sixth edition of the Pharmacopeia.

In the seventh edition (U. S. P. of 1890) this plan was still further elaborated. In the eighth edition (U. S. P. of 1900) there was added what has come to be known as the purity standard or purity "rubric," which is placed in large type immediately before the description, and which defines the percentage of small quantities of permissible innocuous impurities that do not materially affect the medicinal action or interfere with pharmaceutic uses.

Before the passage of the pure food and drugs act of June 30, 1906, conformance with the standards of the U. S. P. on the part of the manufacturers was purely voluntary. Since that time it has become compulsory and the manufacturers recognize its authority. As long as the standards adopted are practical, manufacturers engaged in the chemical and pharmaceutic industries will continue to favor a strict application of the law, and it is safe to state that they would seriously object to its repeal.

But there is another class of manufacturers dealing with materia-medica products, namely, the retail druggists, who are vitally interested in the question of standardization as applied to so-called galenical preparations, namely, preparations of vegetable drugs, such as tinctures, fluidextracts, extracts, pills, etc. The great question which the Pharmacopeial Convention of 1890 and its Committee of Revision had to face pertained to the standardization of vegetable drugs and galenical preparations. The principal opposition came from the retail druggists, who believed that the adoption of standards for galenicals would seriously injure the retailers professionally and financially. They prophesied that their business of manufacturing these products would be taken away from them by the great manufacturing houses, if such standards were adopted, and their vocation would be wiped out.

However, these objections were finally overcome, and standardization was extended more generally to galenical preparations.

The results proved so beneficial to all concerned that the Convention of 1900 instructed the Committee of Revision to "append assay processes to as many of the potent drugs and preparations made therefrom as it may be found possible, providing that the processes of assay are reasonably simple both as to methods and apparatus required, and yield fairly uniform results in different hands." It thus became incumbent upon the Committee to make a thorough study of many assay processes, which led to the introduction into the present Pharmacopeia (eighth) of assays for the following twenty drugs and their thirty-seven galenical preparations: aconite, belladonna leaves, belladonna root, cinchona, red cinchona, coca, colchicum corm, colchicum seed, conium,

guarana, hydrastis, hyoscyamus, ipecac, jalap, nux vomica, opium, physostigma, pilocarpus, scopola, and stramonium.

There are several potent and important drugs which do not admit of standardization by chemical assay and are therefore not included in this list. I refer to epinephrin, digitalis, apocynum, convallaria, geranium, squill, strophanthus, ergot, cannabis, antitoxins, serums, vaccines, etc. During the past two decades physiologic or pharmacodynamic methods have been sufficiently perfected to warrant the introduction of more of them into the Pharmacopeia, now undergoing revision.

The necessity for such standards becomes the more apparent when one realizes the enormous differences in the amounts of active principles in vegetable drugs.

One of the most important drugs in the Pharmacopeia is digitalis. Digitalis varies widely in the amount of glucosids present, so that the tinctures of digitalis on the market are far from uniform in composition. It is well known that this variation is as high as 300 or 400 per cent. The tinctures of strophanthus on the market may vary 6000 per cent. in strength.[1] Many other drugs show wide variation and preparations from them are far from uniform in composition. The chemical assay and standardization of some of the most important drugs is impracticable, owing to their peculiar constitution. Digitalis is one of these drugs. Ergot is another. Methods of physiologic standardization have therefore been adopted for insuring the activity and to a certain extent the uniformity of their preparations. The subject of physiologic and pharmacodynamic standardization will be taken up under its proper head.

Steps in Standardization.

The Question of Nomenclature.—The first step in standardizing a drug consists in giving it a name conformable with scientific nomenclature. Every medicinal drug, chemical and pharmaceutic preparation must of necessity be provided with a name by which it may be recognized and specifically designated. As progress in the science of materia medica and in the pharmacologic arts is dependent upon the impartial discussion of the drug or preparation in question by persons expert in the knowledge of pharmacognosy, pharmacy, pharmacodynamics, and pharmacotherapy, it logically follows that the name must be regarded as common property and equally free to all who have a right to make and sell the product under discussion.

Tests for Identity.—The next step consists in providing tests for identity. The name of the product must always mean the same identical thing, or there can be no standard.

Tests for Purity.—The next step consists in fixing tests for purity. Adulterations, sophistications, and impurities remaining in the products, due

[1] Edmunds and Hale: Hyg. Lab. Bull.

to want of care or to neglect of means for their removal, must be considered and tests which will guard against them generally adopted.

Standardization also consists in reducing this knowledge to the law, embodying it in system, and teaching it to the medical and pharmaceutic professions by means of schools and the press.

It is necessary that educational institutions shall be protected from the dangers of teaching the errors of commercial exploitation. This can only be accomplished by limiting the materia-medica supply business to licensed practitioners, properly qualified by education and training to select, prepare, preserve, compound, and dispense medicines and apply them to the treatment of the sick. No exception should be made for the so-called proprietary-medicine interests. No exception should be made for wholesale druggists or jobbing houses. The entire business should be under the control of persons who are properly qualified and licensed to practise, whether such practice is conducted at wholesale or retail.

Dependent upon drug standardization is the Pharmacopeia; dependent upon this is the very existence of pharmacy, and upon this depends drug therapeutics. Without standardization, medicine would go back to the condition of the Indian medicine man and the conjuring priest; without it pharmacy would return to the condition of the ancient apothecary, who dispensed his herbs and ointments to an ignorant and credulous public and created a demand for his wares by mystery and pretense.

Opposed to drug standardization are ignorance, credulity, and greed; opposed to it are those who regard pharmacy as a commercial business in drugs and medicines, and who create a demand by misleading claims of curative value, whether orally or by printed labels, circulars, or advertisements; opposed to it are all who are exploiting the sick-room for gain.

To sum up: Drug standardization, in its large and comprehensive meaning, consists in fixing a nomenclature for medicinal drugs, chemicals, and pharmaceutic preparations; in providing methods for insuring uniformity in composition, in physiologic action, and therapeutic effect; in adjusting finished products to fixed standards and in devising means for keeping them there for a sufficient length of time to permit their proper application as therapeutic agents; in reducing this knowledge to law and embodying it in system, that we may have a science of materia medica; in embodying this knowledge in textbooks and teaching it to the medical and pharmaceutic professions, so that it may be used by physicians and pharmacists in the practice of their respective arts. Therefore, the importance of drug standardization cannot be overestimated.

Methods of Standardization.

Having considered the meanings of the term "Drug Standardization," let us now consider the modern methods employed for standardizing drugs and rendering them instruments of precision.

1. *Chemical Standardization* means adjustment to adopted standards of purity and strength as determined by the application of chemical processes. It includes the determination of the identity, purity, and strength of medicinal chemicals by qualitative and quantitative tests, and the estimation of active principles in drugs by chemical assays.

2. *Pharmacognostic or Botanic Standardization* is illustrated by the official definitions of drugs given in the Pharmacopeia. When the Pharmacopeia defines cascara sagrada as the "dried bark of *Rhamnus Purshiana*" it means that and nothing else. No other species of *Rhamnus* or other part of the plant may be substituted without danger of prosecution under the pure food and drug laws. Therefore, cascara sagrada is botanically standardized by the Pharmacopeia.

3. *Pharmacologic or Physiologic Standardization* may, in a general way, be applied to all medicinal drugs and chemicals and preparations of the same, including antitoxins, serums, vaccines, and other so-called biologic products. It consists in qualitatively determining the potency or drug power upon healthy living tissues for the purpose of ascertaining whether the drug is active, and, whenever possible, in measuring quantitatively the activity, and adjusting the product accordingly to a fixed and definite standard of strength.

Pharmacodynamic standardization is particularly applicable to the following drugs:—

1. The heart group: digitalis, strophanthus, apocynum, squill, epinephrin, aconite, and gelsemium. 2. Ergot. 3. Cannabis. 4. Antitoxins, serums, etc.

The methods available for standardization of vegetable drugs are as follows:—

a. Toxic method. For this purpose frogs, guinea-pigs, or other animals are used. Examples are Houghton's frog method, Hatcher's cat method, and the guinea-pig method of Reed and Vanderkleed for standardizing the heart group.

b. Method of determining the amount of drug or preparation required to produce some specific effect upon the normal animal. Examples are the cock's-comb method for ergot; the assay of cannabis indica by testing its activity upon dogs; the blood-pressure method for standardizing epinephrin, ergot, digitalis, etc., and the uterine method of standardizing ergot.

c. Method of determining the amount required to produce a definite effect upon an isolated organ. Examples: the isolated-uterus method for testing ergot, and the perfusion method for the heart group.

d. Certain *methods* may be *combined for checking purposes,* as indicated in the following table[2]:—

2 Reed and Vanderkleed: Amer. Jour. Pharm.

Preparation.	Chemical aasay: Gm. digitoxin in 100 c.c.	Physiologic assay: Amount to kill 240-Gm. pig in 2 hours.	Product of figures of columns 1 and 2.
1. U. S. P. tincture	0.0377	0.6 c.c.	0.02262
2. U. S. P. tincture	0.023	1 to 1.25 c.c.	0.02587
3. U. S. P. tincture	0.0277	0.75 c.c.	0.02077
4. U. S. P. tincture	0.0254	1 c.c.	0.02540
5. Fat-free tincture	0.027	1 to 1.25 c.c.	0.02025
6. Fluidextract	0.264	0.1 c.c.	0.02640
7. Fluidextract	0.2405	0.09 to 0.1 c.c.	0.02285
8. Fluidextract	0.234	0.08 c.c.	0.01872
9. Powdered extract	(1.061 per cent.)	0.019 to 0.025 Gm.	0.02334
			Average. 0.02291

e. The Bacterial-count Method of Standardization is used in preparing bacterial vaccines. The counting may be readily accomplished by using a microscope fitted with an Ehrlich eye-piece, and counting the number of bacteria and red blood-corpuscles in a smear made from a mixture of equal parts of blood and bacterial emulsion. Several counts are made of corpuscles and bacteria, and the columns are added. Then by the equation: the total number of red corpuscles is to the amount of bacteria as 5 million (the number of red corpuscles in 1 cu. mm. of blood) is to x, the number of bacteria in 1 cu. mm. of bacterial emulsion is determined. This, multiplied by 1000, gives the number per cu. cm.

f. Standardization by Testing for the Absence of Contaminating Bacteria.—Anthrax vaccine, antistreptococcic serum, rabies vaccine, and the tuberculins are tested in this manner.

g. Serologic Standardization.—The strength of antidysenteric and of antimeningitis sera, the Noguchi test for syphilis, and the Bass test and Widal reaction for typhoid fever are determined serologically.

h. Therapodynamic Standardization is dependent upon the study of diseased tissues in contradistinction to pharmacodynamic standardization, which is dependent upon the study of drugs on healthy tissues. Testing the activity of tuberculin upon persons known to be infected with tubercle bacilli is an example.

i. Clinical Standardization is closely related to therapodynamic standardization, from which it differs in one respect, namely, that the object of therapodynamic standardization is to determine the activity of individual lots of the drug or preparation tested by observing, and if possible measuring, its effects upon diseased tissues, while the object of clinical standardization is to determine the value of a drug as a therapeutic agent.

Classification.

The following tabulated classification of the subject of my paper has been in use during the past winter in lecturing to students at the Philadelphia College of Pharmacy, Temple University, and the Pharmaceutical School of the Medico-Chirurgical College of Philadelphia:—

DRUG STANDARDIZATION.

I. General definition:—
Any and all methods for improving the character, quality, and strength of drugs.

II. Specific definition:—
Adoption of definite standards for drugs and conformity thereto.

III. Necessity for standardization:—
Wide variation in drugs and preparations due to:—
(*a*) Adulteration or sophistication.
(*b*) Impurities.
(*c*) Variation in active principles (ex.: tincture of digitalis varies 300 per cent.; tincture of strophanthus varies 6000 per cent.).
(*d*) Ignorance of collectors.

IV. History of standardization in the U. S. P. from 1890 to 1910.

V. Methods of standardization:—
1. Chemical.
(*a*) Qualitative tests.
(*b*) Quantitative assays.
2. Pharmacognostic or botanic.
(*a*) Official definition of U. S. P.
3. Pharmacodynamic or physiologic.
(*a*) Meaning
1. Testing activity (qualitative).
2. Testing amount of activity (quantitative).
(*b*) Classes of drugs to which applicable:—
1. *Heart group:* digitalis, strophanthus, apocynum, squill, convallaria, epinephrin, aconite, gelsemium.
2. Ergot.
3. Cannabis.
4. Antitoxins, serums, etc.
(*c*) *Methods for standardization of vegetable drugs:*—
1. Toxic method.
2. Determining the amount of drug or preparation required to produce specific effect upon the normal animal.
3. Determining amount required to produce a definite effect upon an isolated organ.
4. Combination of methods for control.
5. Bacterial count method.
6. Standardization by testing for the absence of contaminating bacteria.
7. Serologic.
8. Therapodynamic.
9. Clinical.
4. Bacterial count.
5. Freedom from contaminating bacteria.
6. Serologic.
7. Therapodynamic.
8. Clinical.

CHEMICAL STANDARDIZATION.

It is obvious that space will not permit a detailed outline or description of the methods of chemical standardization in this paper, nor indeed does its scope render this necessary. Methods for the determination of the identity,

purity, and strength of medicinal chemicals and standards for them are well exemplified in the United States Pharmacopeia, and the extension of this work to the unofficial materia medica, new and old, is rapidly being brought about by the American Medical Association and the American Pharmaceutical Association,—the former through its Council on Pharmacy and Chemistry, and the latter through its Committee on Unofficial Standards. The Council of the American Medical Association publishes annually a revised edition of "New and Non-official Remedies" which, though by no means complete, includes a very large number of the more important newer remedies, both uncontrolled and proprietary, providing them with tests for identity, purity, and strength and establishing standards. On the other hand, the Committee on Unofficial Standards is doing for practically all the older products used in medicine not official in the Pharmacopeia what the Council is doing for the newer remedies, providing them with accurate nomenclature, descriptions, and standards, and outlining chemical tests for identity, purity, and strength. The monographs bearing on these products are now appearing in installments in the official journal of the American Pharmaceutical Association, and when completed will form, together with "New and Non-official Remedies," a most valuable adjunct to the United States Pharmacopeia now undergoing revision.

Neither will it be possible to enter here into a detailed description of the various chemical processes used in pharmaceutic assaying, *i.e.*, the estimation of the medicinally active constituents of drugs and their preparations. The actual methods used are well exemplified by the official directions for the assay of such drugs as belladonna, cinchona, nux vomica, and opium. There are, however, certain general facts and underlying principles concerning which the therapeutist should have knowledge, and in discussing pharmaceutic assaying by chemical means it is our purpose briefly to consider these general truths.

Pharmaceutic assaying may be defined as the art of determining the amounts of medicinally active constituents of drugs and their preparations. As such it is an exceedingly important link in the chain of progress which is so rapidly binding together medicine and pharmacy under the inclusive science of pharmacology. Progress in therapy is largely dependent upon the uniformity of the medicinal agents which physicians employ. The absolute necessity for the standardization of pharmaceutic products is therefore apparent. The argument that therapeutists must experimentally determine the proper dosage of an agent to fit the needs of each particular case is no excuse for the tolerance of variation in the strength and potency of the remedy itself; every possible variable should be eliminated in an effort to reduce therapeutics as nearly to an exact science as is possible.

The first requisite for the chemical standardization of complex vegetable drugs and their preparations, therefore, is to know exactly what the "medicinally active constituent" or "constituents" are. For this reason it is highly important that pharmaceutic assaying be developed and improved by the cooperation of the chemist and the pharmacologist.

It must be remembered that the principal end to be accomplished by the

assay of a preparation is to secure a *means of measuring its therapeutic activity.* Hence an assay fails of its purpose unless some direct and constant ratio exists between the figures obtained by the assay process and the therapeutic activity.

Having secured such a ratio, the assay process then, and only then, becomes of value. However, when a fairly constant ratio has been established between the results of an assay process and pharmacodynamic activity, such process becomes of unquestioned value,—whether or not the constituent actually determined represents the entire activity of the drug, or even whether or not it be the principal medicinal constituent. The physician is not concerned directly with the actual percentage of alkaloid, or glucosid, or resin which a drug or preparation may contain: he is concerned only that the adjustment of a preparation to such a percentage of alkaloid, or glucosid, or resin guarantees to him that this preparation will, under similar conditions, produce the same therapeutic effect that any other sample similarly adjusted will produce. We emphasize the fact, therefore, that *any assay process* or *any means of standardization* that *tends to establish a uniform ratio between results obtained and therapeutic activity* becomes at once of unquestionable value, and continues to be of value until supplanted by a new or improved process which more closely maintains this ratio.

For example, Reed and Vanderkleed have shown that the percentage of digitoxin in digitalis and its preparations bears a fairly constant relationship to the activity of the drug, as shown by its minimum lethal dose in guinea-pigs. Although digitoxin is not the only active constituent of digitalis it follows that the chemical determination of digitoxin must be considered of value in the standardization of this drug until chemists have perfected methods for the assay of both digitoxin and digitalin. On the other hand, the determination of the total alkaloids in ergot, although of value in rejecting an inferior quality of drug, cannot be used *alone* as a means of standardizing preparations of this drug, since the proportion of active and inactive alkaloids varies and they do not necessarily bear any very constant ratio to other active principles which may be present.

But few drugs contain one single active constituent that represents its entire medicinal value. Therefore, it will always be impossible in practice to make the results of chemical assay *absolutely* indicative of therapeutic value. But in many cases nature has been kind enough to regulate the proportions of the two or more active constituents in the crude drug within such narrow limits of variation as to enable us to secure invaluable information by determining total alkaloids or some one readily isolated single constituent. Thus in the assay of nux vomica for total alkaloids—strychnine and brucine—the results obtained are of value because of the fact that the important strychnine and relatively inert brucine are present always in nearly equal amounts. On the other hand, gelsemium contains two (possibly three) alkaloids which vary not only in activity, but in their relative proportions in different lots of the drug. The chemical assay of gelsemium for total alkaloids therefore is of but little use for purposes of standardization unless checked and verified by biologic tests.

A discussion of chemical standardization such as this would be incomplete unless there be pointed out the utmost necessity for assaying and adjusting to standard strength preparations such as tinctures, extracts, and fluidextracts, even when prepared from assayed drugs. The variations incident to the manufacturing processes are such that, even with the most modern facilities and with the exercise of the greatest skill, no absolute dependence upon uniformity of result is justifiable without subjecting the finished preparation to final assay and adjustment.

Another exceedingly important consideration for the therapeutist is that of the possibility of deterioration. Of what use is standardization to the physician if the carefully adjusted preparation shall have lost part or all of its activity before it is placed in his hands for use?

Fortunately, only a few drugs and their preparations are subject to rapid deterioration. While no preparation should be looked upon as permanent, and freshness is always desired, the preparations of most of the alkaloidal drugs are quite stable, and fluidextracts of such drugs as belladonna, nux vomica, cinchona, ipecac, and opium will remain potent and reliable for years, if kept tightly stoppered in a cool place. On the other hand, digitalis, strophanthus, and ergot preparations, particularly the latter, deteriorate quite rapidly under the ordinary conditions under which galenical preparations are kept. It is important to insist upon the use of preparations of these drugs which have not been repeatedly exposed to the air by the opening and closing of the stock-container. Small, well-filled sealed packages keep much better than bulk stock, and the future will undoubtedly find preparations, particularly of ergot, dispensed only in vacuum ampoules.

The Standardization of Biologic Materia Medica.

The state of our knowledge with regard to the pathogenesis of disease; the exact relation of the infecting bacteria to the tissues in which they are growing; the identity of the substances by means of which they exert their effect, and the part played in the course of the disease by products of the tissue themselves, and, furthermore, by the products of the interaction of the cellular and bacterial substances, all serve to complicate the problem of specific therapeutics.

Diphtheria and Tetanus Antitoxins.—The pathogenic effect of diphtheria and tetanus bacilli is exercised by means of soluble poisons, the bacteria themselves causing insignificant local disturbance. The toxins produced by these bacteria may be prepared artificially by well-known methods. These artificially prepared toxins are used for the treatment of animals, usually horses, to produce prophylactic and therapeutic serums. The action of these serums is directly against the toxins, the poisonous properties of which are neutralized. The reaction is probably a simple one of a chemical nature, although concerning this latter point there has been some discussion. The relative toxicity of the diphtheria and tetanus poisons, respectively, is determined by animal injection. Definite quantities are injected subcutaneously into guinea-pigs and the characteristic effect observed. The smallest amount which will kill

a guinea-pig on exactly the fourth day is called the minimal lethal dose. Knowing, then, the minimal lethal dose of one of the toxins, it is a simple matter to titrate antitoxin against toxin. The guinea-pig is used as the indicator. If the animal lives, the toxin has been neutralized; if it dies, toxin is in excess.

Such a simple method was first used by Behring. On account of the relative uncertainty of death when the test animals received only one minimal lethal dose, it was found advisable to use a multiple of the minimal lethal dose and 10 minimal lethal doses were decided upon. To this amount antitoxic serum was added in graduated quantities, and the quantity which would prevent the occurrence of all local and general symptoms of intoxication was called a tenth of a unit. Swelling at the point of inoculation could not always be eliminated, even when the toxin was entirely neutralized, and it was decided to consider the *death* of the animal the deciding point. The test was positive if the animal lived beyond the seventh day. Ehrlich showed, however, that this method was open to serious objection, because the toxic diphtheria broth contained not a simple poison, but a very complex one.

Test for Sterility and Safety.—The tests for harmlessness and sterility are of more importance than any other factor in the preparation of the bacterial vaccines. Substances intended for injection beneath the skin must be prepared with infinitely more care than those intended for oral administration. Extremely dangerous substances taken by mouth may generally be recovered, or their effects neutralized by well-known means, but when a harmful or infected substance has been injected beneath the skin it is impossible to recover it. Relatively few of the pathogenic bacteria are able to resist the germicidal action of the gastric juice, but the subcutaneous tissues are susceptible to practically all of them. Our tests, then, must assure us that the vaccine contains no substance poisonous or harmful in itself, and they must demonstrate the absence of all living bacteria and spores.

Subcultures from the various products are therefore of paramount importance. The medium on which these are made must so dilute the preservative that its direct antiseptic action can have no influence upon the development of any living bacteria or spores that might be present. For this reason subcultures on agar or other solid media cannot be used; they must be made into a suitable *fluid* medium. Furthermore, the subcultures must be made under conditions which will favor the development of anaërobic bacteria and spores, as well as aërobes, because the most dangerous organism that may gain access to the vaccine is an anaërobe and a spore-producer. This organism is the tetanus bacillus, and it is so ubiquitous that it must never be considered absent without proof. Then a culture medium in a tube or vessel which will favor the development of the tetanus bacillus should be suitable for subcultures from bacterial vaccines. Bouillon in ordinary fermentation tubes seems to answer all requirements. The tetanus bacillus will develop readily in a fermentation tube containing preferably 1 per cent. dextrose bouillon, provided it has been freshly sterilized. Under these conditions the closed arm is sufficiently protected from air to favor the growth of anaërobes.

As to whether or not tetanus spores might develop any doubt is removed if a small piece of guinea-pig liver or heart-tissue, as recommended by Theobald Smith, is crowded into the bend of the fermentation tube. The fermentation-tube subcultures must be incubated at least forty-eight hours before an opinion may be given as to whether or not the vaccine is sterile. The naked-eye appearance of the tube is not sufficient, because the growth of tetanus bacilli and any flocculent material at the bend of the tube must be studied under the microscope.

It has been found that, if horses be bled while in the early stages of tetanus before the development of symptoms, the serum of such horses may contain sufficient toxin to make the ordinary dose fatal. To detect tetanus toxin or any other harmful substance in the serum it is sufficient to inject 5 c.c. of the serum or other product beneath the skin of a guinea-pig. The animal should be held under observation for about ten days.

While tests may show that the product itself is entirely sterile and free from any contaminating substances, extraneous bacteria may gain entrance to the product while it is being bottled or placed in containers in which it is distributed for use. Check sterility tests should therefore be made at every point during the filling, and the contents of one or more finished containers, selected at random, should be injected beneath the skin of a guinea-pig.

It is felt that these tests are really of more importance than tests for strength, since an uncontaminated substance, even though it is low in potency, may do no harm, while a contaminated antitoxin, while very high in efficiency, may result in more harm than good. Even slight accidents of this kind are pounced upon and magnified by those persons of peculiar mental equipment who believe it is their duty to object to everything not the result of their own vain imaginings.

Pharmacognostic or Botanic Standardization.

In a lecture delivered before the Section of Pharmaceutical Sciences of the French Association for the Advancement of Science, at Dijon, August, 1911, Prof. A. Tschirch, Director of the Pharmaceutical Institute of the University of Berne, called especial attention to the importance of modern pharmacognosy in the study and standardization of materia medica. Schleiden, the great botanist, called pharmacognosy "the mother of all the natural sciences," and, while Tschirch admitted this to be "a rather exaggerated phrase," yet he demonstrated by his historical references the great influence of pharmacognostic study in the development of the natural sciences.

"There is no doubt," said this great authority, "that man, before studying pure chemistry and botany, first studied the chemistry and botany of medicinal and toxic plants, that is to say, the products of nature which were most immediately useful to him. Theophrastus and Dioscorides, whom I should like to call the first pharmacologists, were at first interested in such plants. During the entire Middle Ages, such scientists as Hildegard and Albertus Magnus, as well as the Arab writers, studied and described only these same plants, and

when the beginning of the contemporary epoch saw the renaissance of all the sciences, the 'Patres Botanices' book, Brunfels, and Fuchs devoted themselves to the study of medicinal plants."

In the nineteenth century pharmacognosy was put aside by the rapid development of the purely theoretical natural sciences and became nothing more than a superficial knowledge of merchandise. But Flückiger and Hanbury opened a broader field for it. To be sure, they regarded it as little more than a monographic study of their drugs, but their work gave it a fresh impetus. This development has occurred during the past ten years. Then Pomet, Geoffroy, Guibourt, Schleiden, Ondemans, Berg, and Tschirch, on the other side of the water, and Kraemer, Schlotterbeck, and Rusby, on this side, gave it new development. Leaving the purely practical, to remain, however, of great importance as applied pharmacognosy, it directed itself to purely scientific problems and has become, during the past decade, an independent science.

Tschirch calls attention to the great divisions and subdivisions into which this great subject may be divided. The botanical questions must be separated from the chemical and physical questions; the geographical and historical questions, from the linguistic and ethnological questions. Thus, we have the separate branches, pharmacobotany, pharmacochemistry, pharmacogeography, pharmacoethnography, and the history of pharmacognosy, the study of which should be directed from general pharmacognostic viewpoints, and not from the viewpoints of botany, chemistry, geography, ethnography, etc.

Turning to pharmacoanatomy, we find its practical bearing upon the subject before us, viz., the modern methods of drug standardization. By the study of this branch we have learned how to ascertain the identity and purity of drugs by examining powdered drugs macroscopically and microscopically. Attention to pharmacophysiology is teaching us how to so cultivate medicinal plants as not only to maintain their active principles at a regular standard, but to increase them. And it is hoped that the time may come when we may succeed in developing in the plants only the valuable active constituents, and in causing the less important principles to diminish. This opens up the field for pharmacoagriculture, including the study of the effects of soil, climatic conditions, fertilizers, and grafting.

That the value of medicinal plants can be increased by intelligent cultivation has been abundantly demonstrated by the culture of cinchona in Java, where the Dutch have succeeded in producing barks yielding 16 per cent. of quinine. The Committee on Revision adopted as its standard for the eighth edition of the United States Pharmacopeia 5 per cent. of total cinchona alkaloids, which will be increased in the next revision to 6 per cent. By cultivation, beets are made to yield 15 to 16 per cent. of sugar. By means of experiments and observations carried on for several years in the forests of Berne by Tschirch, he was enabled to formulate a law which he called the law of resinoids. When this law was tested in the forests of North America an increase in receipts of $100,000 resulted for the rosin manufacturers in one small district.

The results obtained with drugs producing alkaloids, saccharine substances, and resins can certainly be achieved with plants containing glucosids, odorous substances, and fatty or mucilaginous materials.

The limits of this paper will not permit extended reference to the action of ferments upon drugs and the wonderful results obtained by killing the ferments by elevated temperatures during the process of drying them. But we cannot leave the subject without calling attention to the warning to the medical profession contained in the following words of Tschirch: "We know that rarely does a single substance suffice to produce the effect of the drug; it is the combined action of all the substances which brings about the peculiar effect. Nevertheless we must often recognize the preponderating influence of one substance, which I have characterized as dominant. It is at first by clinical experience that one gets to appreciate this fact, since it has thus been determined that the effect of employing the entire drug is rarely the same as the effect of the single so-called active principle. Moreover, Professor Bürgi, of Berne, has shown positively that very often the effect of one substance can be augmented or diminished by another, and that similar substances are not additive in their effects. The 'adjuvantia' of the old pharmacologists were therefore not chimeras, but, on the contrary, a distinct idea corresponding to the name and to the thing itself.

"This ancient idea, under a new form, brings us to the study of the drug itself. Under the influence of the successes of the modern synthesis of medicaments, and the misunderstood theory of the so-called active principle, we have been gradually abandoning drugs, in spite of experiments carried on for hundreds of years, and even, in the case of certain drugs, for thousands of years. Many physicians have already disaccustomed themselves to the use of drugs. But they cannot be replaced, and the wish that I expressed in London, in 1909, 'let us go back to drugs' found an echo much sooner than I expected, and in more extended circles than I had dared hope.

"How can one replace rhubarb by a solution of emodin, ipecac by emetine, opium by morphine, digitalis by digitoxin, ergot by ergotoxine or by the interesting bases isolated by Barger and Dale, which, according to the recent experiments of Kehrer, do not even act on the uterus? Emodin, emetine, quinine, digitoxin, and morphine are pharmacological individuals, different from the drugs themselves, and should be numbered among remedies not to replace the drugs, but to stand beside them.

"Since we know that there is in the drug a dominant principle, but that the effect is not produced by this principle alone, we are more than ever obliged to make a profound chemical study of the drug in all its elements. The object of pharmacochemical research is not the discovery of a single active principle, but the complete analysis of the entire drug."

Pharmacodynamic or Physiologic Standardization.

Physiologic or, more properly, biologic assays are of value in two ways, —first, when they must serve alone in the absence of any available chemical

method, and, secondly, to supplement and to check the accuracy of conclusions based upon chemical standardization.

The purpose of the biologic assay, just as of the chemical assay, is to secure a means of measuring therapeutic activity and to make it possible to furnish *uniform* preparations. A satisfactory method which meets these requirements may or may not involve the production of physiologic reactions similar to those which the drug is intended to be the means of producing when used therapeutically. That the effect chosen as a means of standardization does not parallel the clinical effect sought is not sufficient to condemn the method. It is only necessary that the effect chosen as an earmark be always indicative of a good quality of the drug or preparation, and criticisms of methods on the ground that they are *toxic* methods or that the animal chosen is biologically much different from man are made only through a lack of conception of the real purpose of the physiologic test, namely, to secure *uniformity*. The determination of the real value of a drug in the treatment of disease in man is another matter entirely.

While many articles have been presented to science during the past few years, dealing with one or more of the biologic methods in use at this time, apparently no attempt has been made to bring them all together in such a manner as to make it possible for one to follow them without referring to many diverse publications. We have accordingly outlined the principal biologic methods of assay in use in standardizing the modern materia medica, and given specific directions for carrying out this work.

Blood-pressure Method for the Standardization of Epinephrin and Products of the Suprarenal Gland.

Apparatus Necessary for Experiment.—A large kymograph with manometer arranged for taking blood-pressure tracings on continuous rolls of smoked paper; accurately graduated all-glass syringe; large and small scalpels; small, sharp-pointed scissors; grooved director; hemostat; two glass seekers; several bulldog clamps; small glass cannulas; silk ligatures; a dog board.

Animals.—Various animals may be employed, the dog, cat, or rabbit; but dogs of medium weight (8 to 14 kilos) give the best results.

Preparation for Experiment.—First completely anesthetize the animal. Any of the volatile anesthetics, such as ether or chloroform, may be employed, but, since it is of great importance that the blood-pressure should not fluctuate from the action of the anesthetic, it is better to employ one of the following methods for this purpose:—

1. Inject subcutaneously 0.01 Gm. of morphine sulphate for each kilo of body weight, and supplement by the use of such a quantity of ether as may be necessary to prevent the pain of the operation. After connecting the artery with the manometer the animal is allowed to come from under the influence of the ether. No experiments should be begun until at least ten minutes have intervened after the withdrawal of the ether.

2. Inject subcutaneously 0.01 Gm. of morphine sulphate per kilo body weight of animals, and 45 to 60 minutes later give by mouth 1.5 to 2 Gm. of acetone chloroform (1.5 Gm. for animals weighing 6 to 7 kilos, 2 Gm. for those weighing 10 to 12 kilos, and intermediate weights accordingly). The acetone chloroform is prepared for administration by shaking it with 4 c.c. of alcohol until dissolved and then adding 4 c.c. of water and again shaking.

The latter method is especially valuable for this work, as it is easily carried out, and under its influence the blood-pressure and heart action remain

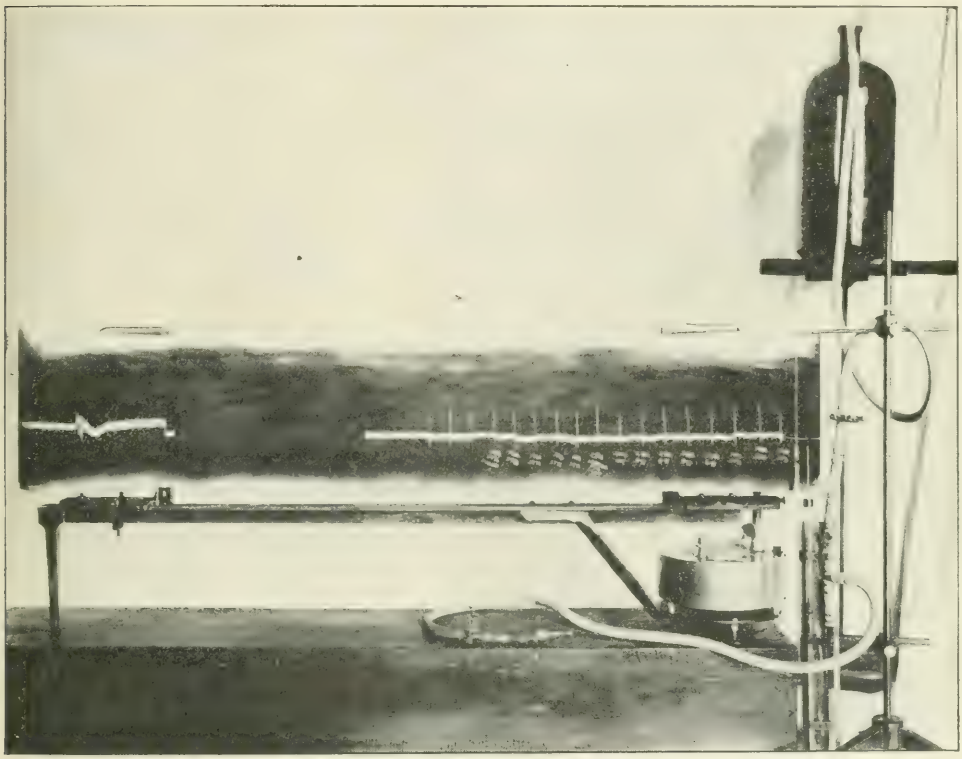

Fig. 1.—Arrangement of apparatus for taking blood-pressure tracing.

practically constant for hours. I find, however, in many cases, that the animal does not react in such a way as to give concordant results immediately after the administration of this anesthetic, and therefore advise the following procedure:—

3. Administer the anesthetic as set forth above; wait until all voluntary movements have ceased; clip hair from the throat; make an incision about 2½ in. long; sever the tissues surrounding the carotid artery in such a manner as to free about 3 in. of it, taking care not to injure the vagus, which is found in the same sheath. Next make an incision about 2 in. long over the saphenous vein at its junction with the femoral vein and sever the tissues just enough to free about 1 in. of each; tie a short cannula of small bore in the saphenous,

close to its junction with the femoral; cover both incisions with a piece of gauze saturated with normal saline solution. *The animal is then left in this condition for 1½ to 2 hours so that the effects of the anesthetic may partially pass off;* remove the gauze from the neck; lift the exposed part of the carotid artery by means of a glass seeker; tie off that part of the artery leading to the brain (Fig. 2, 1) and close that part leading to the heart with a "bulldog" clamp (2), leaving at least 2 in. between the ligature and the clamp; snip a small V-shaped hole in the artery (*a*), about ¼ inch from the ligature, with sharp-pointed scissors; make sure that the connecting tube (*b*) and cannula (*d*) are free from air; insert cannula in hole (*a*) and tie the artery fast by means of another ligature (Fig. 2, *Z*). Open *C* (Fig. 3) and *E* in order to fill the portion of the artery between the cannula and the bulldog clamp with the magnesium sulphate solution. This keeps the blood from entering the cannula and thus prevents clotting; close *E;* close *C;* remove clamp from artery;

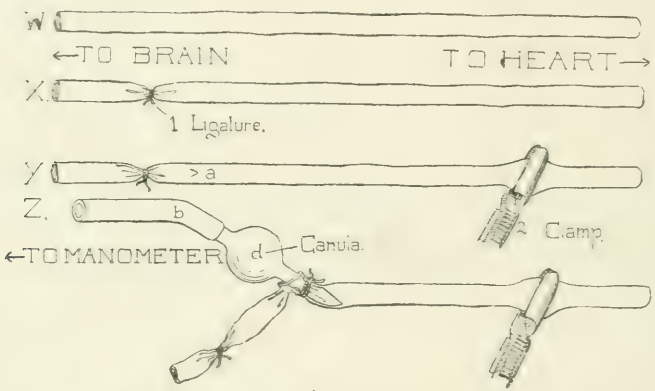

Fig. 2.—Method of connecting the artery with the manometer.

slowly open *C* until the floater *F* makes an excursion of about ⅝ to ⅜ in. It should then be made to write on a drum which will revolve slowly,—about 1½ to 2 in. per minute.

Preparation of Solutions.—The standard solution is prepared by dissolving 1 part of pure epinephrin hydrochloride in 100,000 parts of normal saline solution.

The preparation to be standardized should be carefully diluted with normal saline solution to the same strength, as nearly as may be estimated, as that of the standard used, or be of such strength as may be readily diluted in case the primary injection is found to produce too marked a rise in the blood-pressure.

Method of Injecting.—The injections may be made either in the jugular or the femoral vein. The latter is preferable because it is located farther from the heart, thus giving the preparation injected an opportunity to diffuse more thoroughly with the blood before reaching the heart.

The saphenous vein is lifted and held with a pair of tweezers while the

needle of the all-glass syringe is inserted far enough through the cannula in the saphenous vein to allow the point to project into the femoral vein (Fig. 4). After injecting the preparation withdraw the needle and quickly clamp saphenous vein with a bulldog clamp.

The advantage of this method is that, although clamping off the saphenous

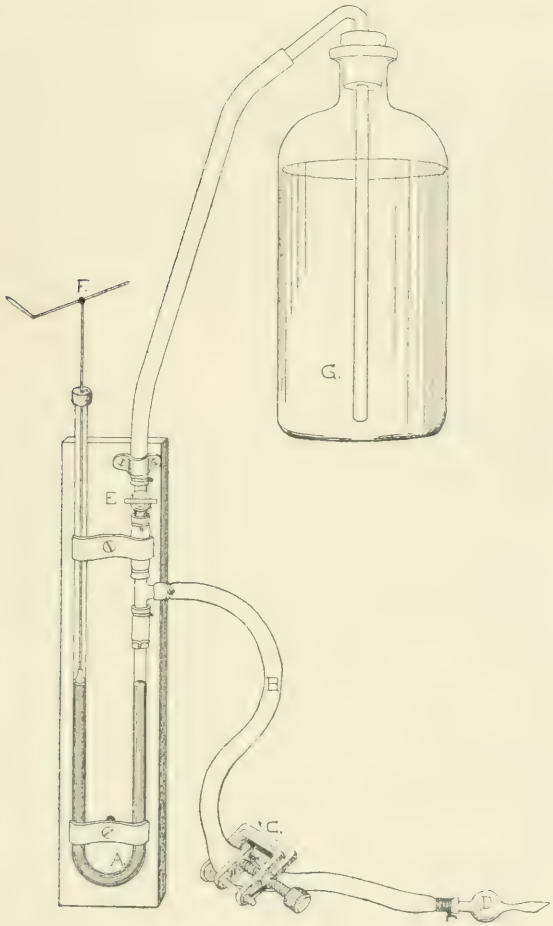

Fig. 3.—Mercurial manometer. (*A*) U-tube partially filled with mercury. (*B*) Connecting tube. (*C*) Screw-clamp. (*D*) Cannula. (*E*) Stopcock. (*F*) Floater with writing point. (*G*) Pressure-bottle containing half-saturated magnesium sulphate, or sodium carbonate, solution.

vein after withdrawing the needle causes clotting, the preparation injected is carried to the heart by means of the main current of blood in the femoral vein.

Actual Standardization.—(*a*) *Determination of the Proper Dose of the Standard Solution.*—The blood-pressure tracing is started on a slowly revolving drum. After obtaining a tracing of normal pressure about 3 in. in length, the drum is stopped. Inject the standard solution in a dose of 0.15 c.c. per kilo. The rise of the blood-pressure should be about 40 to 60 mm. of mercury

(equivalent to 20 to 30 mm. rise of the writing point of the floater in a U-shaped manometer), and it should be submaximal. To determine the latter, a second injection of 0.175 c.c. per kilo should be made after allowing the drum to revolve about 1 in., which should show a higher rise. If the dose of 0.15 c.c. per kilo does not give a submaximal rise of at least 40 mm., or if it gives a maximal rise, the dose should be increased or reduced, respectively, until the standard effect is obtained, and this dose should be considered the "standard dose." The injections should be made at about the same rate, and an interval of at least 3 minutes should elapse after the blood-pressure has returned to normal before another injection is made.

The "standard dose" should be large enough to cause *almost* the maximum rise, because the larger the amounts of active principle compared the more accurate the results. It is well known that the stronger the stimulus the more nearly in accord are the results obtained.

(*b*) *Comparison of the Unknown with the Standard Solution.*—A "stand-

Fig. 4.—Method of injecting. (*a*) Femoral vein. (*b*) Saphenous vein. (*c*) All-glass syringe.

ard dose" of the unknown solution is injected and the rise of pressure compared with that produced by the "standard dose" of the standard solution. If the difference is very great the unknown solution is strengthened or diluted. The amount of the injections is then increased or decreased until that dose of the unknown solution is found which will cause the same rise of pressure as that caused by the "standard dose" of the standard solution. Occasional injections of the standard solution should be made to insure constancy in the reaction of the animal. Final equality is tested by injecting alternately the standard and unknown solutions until the average rise of several consecutive injections is practically equal.

Complete and Abbreviated Tracings.—Two kinds of tracings may be obtained.—(1) complete ones, when the drum is kept in constant motion, and (2) abbreviated ones, when the drum remains at rest until the reaction is complete. Abbreviated tracings which give only the maximum blood-pressure obtained from each injection are usually sufficient.

In measuring the tracings it must be remembered that the real rise in blood-pressure is twice that which is recorded, since there are two sides to

the U-tube and the needle only moves through a space that represents the difference of level between the mercury in the two sides.

It is understood that no calculations are to be made from relative size of rises caused by similar doses, but always from similar rises, the relation being determined by the size of the dose. More accurate results are obtained if the systolic pressure is alone considered than if the average pressure half-way between systole and diastole is taken for the measurement.

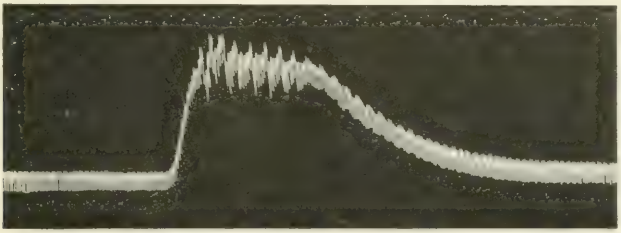

Fig. 5.—Complete tracing.

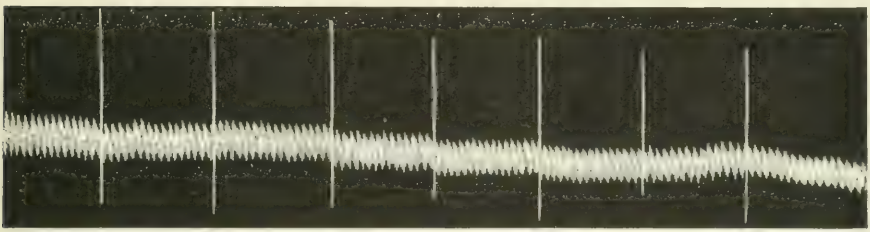

Fig. 6.—Abbreviated tracing.

Standardization of Ergot.

Three principal methods are available for the physiologic standardization of ergot:—

1. The Blood-pressure Method.
2. The Cock's-comb Method.
3. The Uterine Method.

These methods are not new, but merely quantitative applications of methods used for the purpose of studying the physiologic action of the drug.

1. Blood-pressure Method.—This is perhaps the most convenient and generally serviceable test. The technique involved is comparatively easy and, unlike other methods, the effects may be graphically portrayed and accurately measured,—thus giving a *definite quantitative standard.* This is a great advantage over the other methods, as *the assay does not require nor depend upon the keeping of a standard preparation which may deteriorate.*

Apparatus Necessary for Experiment; Animals; Preparation of Experiment.—Same as required for the standardization of epinephrin.

Preparation of Solutions.—All preparations to be tested should be carefully diluted until 1 c.c. of the dilution represents 1 Gm. of drug.

Method of Injecting.—Same as that given under Epinephrin Standardization.

Actual Standardization.—The blood-pressure tracing is started on a slowly revolving drum. After obtaining a tracing of normal pressure about 3 in. in length, the drum is stopped. An injection of 0.04 c.c. (Gm. of drug) per kilo of the preparation to be tested is then given and the blood-pressure observed for ten or fifteen minutes. In most cases the injection is followed by a

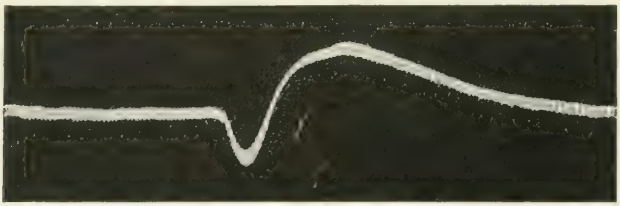

Fig. 7.—Complete Tracing.

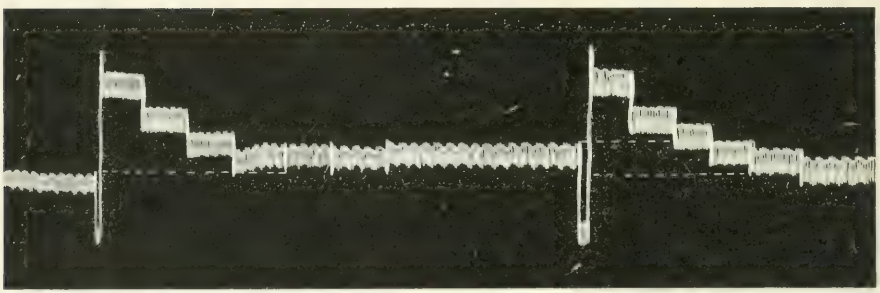

Fig. 8.—Abbreviated Tracing.

rapid primary fall of pressure, succeeded by an almost equally rapid rise to normal or above,—according to the strength of the preparation. In order to facilitate the measuring of the myograms, the drum is made to revolve a short distance as follows:—

1. When the point is reached where the blood-pressure is about to rise after its primary fall.
2. Five minutes after the injection.
3. Ten minutes after the injection.
4. Fifteen minutes after the injection.

Myograms Showing Effect of Ergot on the Blood-pressure.—If the first injection causes a fall of pressure of more than 35 mm., or a rise of more than 48 mm., the dose should be reduced to 0.02 c.c. per kilo. If the fall is less than 24 mm. and the rise less than 24 mm. the dose should be doubled; otherwise, the same dose is repeated.

Three to four injections are given to one animal, allowing from sixty to ninety minutes to elapse between injections in order to allow the effects of the previous injection to pass off.

Use of Several Animals.—Three or four injections of the same preparation should be made into each of three or more dogs and the average rise of pressure taken as the figure of potency.

In order to express the activity of the preparation in percentages it is necessary to adopt some provisional standard with which to compare the unknown preparation. After much experience we have adopted the following standard for our laboratory:—

"0.08 c.c. of the fluidextract per kilo should cause a rise of blood-pressure of 30 mm."

An objection to this method is that mongrel dogs, such as run at large in the city, differ considerably in their reaction, but, by using at least three dogs for each preparation of ergot, this source of error is considerably reduced.

2. The Cock's-comb Method.—This method was formerly regarded as very unreliable because of the difference in susceptibility of various cocks. Some years ago Edmunds was unfavorably impressed with this method and discarded it, but after more extensive experience he stated, in a paper with Hale,[3] that accurate results may be obtained by this method if only white Leghorn cocks are used, since the common barnyard fowl varies too greatly in its reaction.

Select healthy white Leghorn roosters of as nearly the same size and age as possible. (Those weighing from 1200 to 1600 Gm. are best.) By means of an accurately graduated hypodermic syringe, inject into the breast-muscles of one cock a dose of a standard preparation. Inject another with the same dose of the unknown preparation, and, one hour after the injections have been given, compare the color of the two combs, as the maximum cyanosis seems to be reached in about that time. The color begins to fade soon after, so that at the end of two hours or more, depending on the amount of drug given, the comb will usually appear to be nearly normal. Judging from the results obtained from the first two injections, the dose *of the unknown preparation* is increased or diminished until that amount is found which will give approximately the same intensity of action as was shown by the color of the comb of the rooster injected with the standard. The same roosters may be used for several tests, but the injections should be made at intervals of two or three days, so as to allow sufficient time for complete recovery from the effects of previous administrations of the drug. It should not be considered sufficiently accurate if the first injections of the standard and of the unknown preparations produce the same degree of activity, because it is believed that individual variation in different birds might be sufficiently great to interfere. In order to reduce this variation to a minimum, the order of injection on the succeeding day should be reversed until each preparation has been given to each of several birds in turn and the results then based on the average of the several injections. The final comparisons demand careful selection of the birds to be injected. A choice of two birds is advisable which are of about the same size and have pre-

[3] Edmunds and Hale, Bull. No. 76, Hyg. Lab. U. S. Pub. Health and Mar. Hosp. Serv.

viously reacted well to the drug. With a little practice it is easy to compare the intensity of the discoloration in the two cocks' combs and so to regulate the dose of the drug given as to produce approximately the same degree of reaction. The doses thus obtained will give the relative strength of the two drugs.

Variations may further be avoided by using only such roosters as react alike to a standard preparation; and also by constantly changing the order of injections so that the same cock shall not receive the same specimen of the drug twice in succession. Although the relative strength of two preparations may be thus determined quite accurately by this method, it is not well adapted for standardization work because it requires that a standard preparation shall be kept on hand. This makes the standard dependent upon the keeping qualities of a stock galenical. Any deterioration, therefore, will result in a lowering of the standard for all subsequent preparations. Owing to the rapid deterioration in preparations of ergot,[4] it is, therefore, practically impossible to keep on hand a preparation of standard strength and it is believed that more satisfactory results may be obtained by the blood-pressure method because the blood-pressure may be accurately measured by the manometer and kymograph, and permanently recorded.

3. Uterine Method.—*Apparatus Necessary for Experiment.*—Myocardiograph, Harvard light muscle lever, counterbalance weights, surgical instruments, cannulæ, tank for saline bath, all-glass syringe, and an apparatus arranged for maintaining artificial respiration.

Animals.—Various animals may be employed, including the dog, cat, and rabbit, but cats of medium size give the best results.

Preparation of Experiment.[5]—When the intact animal is to be used it is anesthetized with acetone-chloroform (0.3 to 0.4 Gm. per kilo of body weight) given in solution by means of a stomach-tube. A cannula is then placed in the external jugular vein for the injection of the drugs, and a tracheal cannula is inserted to allow artificial respiration, which is kept up during the entire experiment. The animal is then submerged in a 0.9 per cent. saline bath maintained at the constant temperature of 39° C. The further operative process of exposing the uterus is then carried out by an incision along the linea alba from the ensiform cartilage to the symphysis pubis and the two halves of the abdominal wall drawn apart and secured by means of hooks. The bladder and intestines are drawn aside and secured underneath the salt solution to prevent any irritation by exposure to the air and drying. One horn of the exposed uterus is then freed as much as possible from its attachment to the posterior wall of the body cavity by tearing away the peritoneal attachments. Especially is it advantageous in securing a uterus with the utmost freedom of movements to detach the ovary by tearing it free from the ligaments binding

[4] Recent investigations by Pittenger and Vanderkleed, soon to be published, indicate that ergot fluidextracts may be kept *in vacuo* without deterioration. This fact will result in making it possible to preserve standards with which to compare new lots of drug and their preparations.

[5] Edmunds and Hale: *Loc. cit.*, pp. 28-29.

it to the posterior wall, although care must be used not to injure the blood-supply in these manipulations.

For the purpose of attaching the uterus to the recording apparatus two silk threads are passed, using a fine round needle, through the uterine horn at a distance of about 2 cm. apart. These are attached to the levers of an ordinary myocardiograph.

For recording the movements a light lever is attached to the myocardiograph, and, as the matter of tension is of great importance, a Harvard light muscle lever is made use of on account of its extreme lightness. Since it has been noted that some uteri will react under considerably more tension than others, the amount of tension is varied by the use of counterbalancing weights until a satisfactory result is secured. These conditions are only attained as a result of experiment with each individual organ, and it is frequently necessary to make a number of injections of ergot, using different degrees of tension on the uterus before the best conditions for comparative tests are obtained.

Preparation of Solutions.—All preparations to be tested should be freed from the greater part of alcohol by evaporation on a water bath and made up to fluidextract strength with normal saline solution.

Method of Injecting.—Same as under Epinephrin Standardization.

Actual Standardization.—"When the mechanical requirements for the experiments are fulfilled the specimens of ergot are injected. More satisfactory results are secured by comparing only two preparations, the unknown and the standard, at a time, injecting them alternately at intervals of not less than five or, perhaps better, ten minutes, and increasing or diminishing the doses until such amounts of the preparation are found which will produce contractions of equal intensity. It is by no means easy to accomplish this, and frequently it calls for the exercise of considerable patience, as, for example, it is not an unusual experience to carry on such an experiment for two or three hours and, on account of the irritability of the uterus as shown by spontaneous contractions, to know very little more about the relative strengths of the two specimens at the end than at the beginning of the experiment.

"In a favorable experiment, for example, one being carried out on the uterus of a virgin cat, there are no spontaneous contractions, and after each injection the uterus responds by a single contraction. In such an experiment it is often possible to get very definite results in a short time, the results from one pair of injections being verified by further injections until there can be no doubt in the mind of the operator as to the relative activity of the two preparations. No standard of comparison can be given, however, which will fit all animals—in the one case the relative strengths of the contraction as outlined above may be taken, while in the second it may be necessary to adopt as an end-reaction the smallest amount of each drug which will produce a contraction, while in a third uterus, which may be irritable and show spontaneous movements, it may be necessary to employ as a standard the smallest amount which will clearly influence these movements, as, for example, by a delay in the relaxation. Thus it will be seen that each animal appears to be a law unto itself, so far as tension is concerned, and also as to the character of the uterine

movements, and that the standard which is to be used in comparing specimens of ergot must be a variable one on that account."

CANNABIS INDICA.

This assay depends upon the characteristic action of the drug upon the central nervous system, in which changes are induced causing a peculiar train of symptoms. These are divided into three typical stages: (1) one of excitability; (2) one of inco-ordination; (3) one of lassitude and sleep.

Shortly after receiving a dose of suitable size of cannabis indica the animal generally vomits and then becomes excitable. In from one to two hours inco-ordination follows; the dog loses control of its legs and of the muscles supporting the head, so that, when standing, the feet are usually spread apart to maintain balance. When nothing occurs to attract attention the head droops and body sways from side to side or anteroposteriorly. A distinct ataxia is present in walking, and, when severely affected, the animal will stagger and fall. If, however, it is spoken to sharply or attention is drawn to anything of interest it may momentarily recover and the typical effects of the drug disappear, but in a few minutes it again relapses into the former condition. As the action of the drug progresses the muscular inco-ordination becomes greater and the animal passes into the third stage; the depression and lassitude are increased until finally the animal sinks to the floor as if exhausted and passes into deep, undisturbed sleep. After several hours the effects of the drug slowly disappear and the normal condition returns.

For standardization purposes the end-reaction to be observed is one just sufficient to produce muscular inco-ordination in a dog.

Animals.—Short-haired dogs of medium size (6 to 12 kilos) are well adapted for this work. They show the different stages of the drug's action because of their comparatively high brain development.

Animals for assay purposes should be selected with great care, it being necessary to pick out those that are healthy, intelligent, quiet, and which have shown by previous tests that they are easily affected by the drug.

After several dogs have been selected, the operator, before using them for actual work, should study each animal in order to familiarize himself with the behavior, peculiarities, etc., of the dog under normal conditions. The same animal may be used many times, provided that twenty-four to thirty-six hours are allowed to elapse between doses in order that the animal may *completely* recover from the effects of the previous dose.

Although the animals never appear to lose their susceptibility, it is not advisable to use a dog for more than six months, and care should be taken to allow one week to elapse between assays.

Preparation of Experiment.—Select and weigh several animals which have been found easily susceptible to the action of cannabis, and withhold all food for at least twelve hours previous to the time of administration of the drug. Water should be allowed.

Preparation of Drug for Administration.—Tinctures and solid, powdered, and fluid extracts are weighed or measured directly into hard gelatin capsules.

When a crude drug is to be tested a representative sample should be finely ground and then made into a fluidextract.

Method of Administering.—The drug is administered internally by means of a small capsule. The animal's mouth is opened by forcing the thumb and index finger of the left hand between the jaws, back of the teeth. The capsule is then placed on the back of the tongue with the right hand and the mouth quickly closed; while still holding the mouth shut, the animal can be made to swallow the capsule immediately by slapping it on the throat.

Actual Standardization.—Administer to a series of three selected dogs $^{9}/_{10}$, $^{10}/_{10}$, and $^{11}/_{10}$ of the standard dose of the preparation to be tested, for each kilo body weight of animal. Then place the animals in a room where they will be undisturbed and are remote from noise and excitement; careful observations should be made and the results recorded during four or five hours.

If this preliminary test shows that the drug is either above or below standard strength, other dogs are given progressively increasing or decreasing doses, as the case may be, until the smallest dose per kilo body weight is found which will produce an action just sufficiently pronounced to bring on the stage of inco-ordination. This is distinguished by a slight ataxia when walking and a drooping of the head and gentle swaying of the body while at rest. The relative strength of the preparation tested is then computed between the "minimum dose" and the "standard minimum dose" by simple proportion.

The personal equation plays an important part in this assay, since the accuracy of the test depends largely upon the experience of the operator and his ability in determining just when the effects of the drug manifest themselves. In the hands of an experienced operator, therefore, results may be obtained which will show, with fair accuracy, the relative value of any preparation of cannabis sativa.

Standardization of Cardiac Stimulants and Depressants.

The most important plants which contain bodies whose physiologic action comes under this head are *Digitalis purpurea, Strophanthus hispidus* or *Kombé, Scilla maritima, Convallaria majalis, Apocynum cannabinum, Aconitum napellus, Veratrum viride* or *album,* and *Gelsemium sempervirens.* These drugs may be divided into two groups as follows:—

1. Stimulants
   - Apocynum.
   - Convallaria.
   - Digitalis.
   - Squill.
   - Strophanthus.
2. Depressants
   - Aconite.
   - Gelsemium.
   - Veratrum.

Several methods are available for the quantitative determination of the activity of these drugs and of their preparations, the three principal type methods being:—

1. A toxic method, in which guinea-pigs, frogs, and some of the higher animals are used,—such, *e.g.,* as Reed and Vanderkleed's Guinea-pig Method;

Hatcher's Cat Method; Famulener and Lyons's "One Hour" Frog Method; Houghton's "Twelve Hour" Frog Method, and Focke's Frog Method.

2. The effect upon blood-pressure.

3. The effect upon the isolated heart of the frog or turtle. (*Example:* Perfusion method.)

1. Toxic Methods.—(*a*) *Guinea-pigs.—Reed and Vanderkleed's Method.*—This method consists in determining the minimum dose per 250 Gm. body-weight of guinea-pig that will prove fatal within 24 hours when the drug is subcutaneously injected.

Apparatus Necessary for Experiment.—One Hitchens's syringe, pipettes, graduated in $\frac{1}{100}$ c.c., scissors, scales and weights ranging from 1 to 500 Gm.

Animals.—Guinea-pigs in good physical condition and weighing from 180 to 400 Gm.

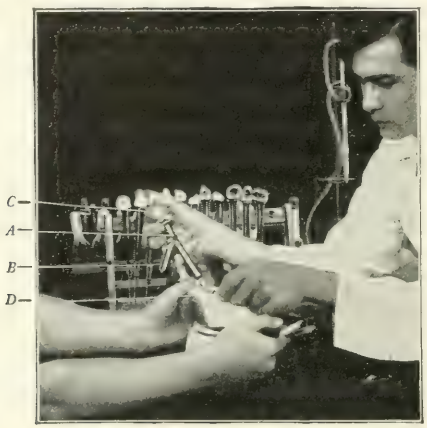

Fig. 9.—Method of Injecting Guinea-pigs. *A* and *B*, glass body of Hitchens's syringe; *C*, detachable bulb; *D*, needle.

Preparation of Experiment.—The guinea-pigs are prepared for the injection by clipping or shaving the hair from about 1 sq. in. of the skin over the abdomen, and painting the exposed portion with 5 per cent. tincture of iodine. The pigs are then weighed and records kept.

Preparation of Solutions.—If the preparation to be tested is a tincture or a fluidextract it should be freed from the greater part of alcohol by evaporation on the water bath, and diluted with normal saline solution to the desired volume. Solid and powdered extracts should be dissolved in a sufficient quantity of a suitable menstruum to render the doses accurately measurable. In all cases the preparations should be sufficiently diluted or concentrated, as the case may be, to make the dose injected measure not less than 0.5 c.c. nor more than 4 c.c.

Method of Injecting.—The injections are given subcutaneously in the abdominal region. The following illustration shows a very simple and handy method:—

The Hitchens syringe shown in the above illustration is especially

adapted for this work because it allows no possibility of loss while inserting the needle and may be washed with water without being withdrawn.

Method.—Pipette the desired dose of the preparation to be injected into the side arm (*B*) of the syringe; while holding the syringe with the side arm down, insert the needle as shown above; rotate the syringe to allow the liquid to run from *B* to *A;* insert rubber bulb (*B*) into neck of syringe and inject the liquid by applying pressure to the bulb with the thumb; remove bulb; wash the side arm with about 1 c.c. of water from a "sprütz bottle"; rotate syringe several times, replace bulb and inject wash-water; massage injected liquid away from the point of injection; withdraw needle.

Actual Standardization.—Inject into a series of four guinea-pigs $^{9}/_{10}$, $^{10}/_{10}$, $^{11}/_{10}$, and $^{12}/_{10}$ of the standard dose of the preparation to be standardized for each 250 Gm. body-weight of guinea-pig. Then place the animals in cages and allow them to remain for 24 hours, when they are to be examined and a note made of those living and those which are dead.

The results of this preliminary test, in which the range of dosage is quite wide, enables the investigator to form some idea as to the strength of the preparation. Basing the dosage upon these results, other series of guinea-pigs are injected with progressively increasing or decreasing doses, as the case may be, still further diminishing the variation between doses, until the smallest amount is found which will prove fatal within 24 hours. The probable minimum lethal (toxic) dose of the preparation, unless it deviates considerably from that of the standard, is generally obtained by one or two series of injections. In order to determine whether or not this is the true minimum lethal dose this result is checked by carefully injecting a new series of 4 pigs; 2 with the smallest dose that was found to kill, and 2 with the largest dose that did not kill. If any of this last series shows irregularities, further correction must be made.

In order to express the percentage results it is necessary to adopt for each drug or preparation assayed a standard minimum lethal dose with which the minimum lethal dose of the preparation being tested may be compared. After long experience we have adopted the following provisional standards for our laboratory:—

Tinctures.		Fluidextracts.		Solid and Powd. Extracts.	
Drug.	M. L. D.	Drug.	M. L. D.	Drug.	M. L. D.
Aconite Root.....	0.1	Aconite Root	0.01	Aconite Root ...	0.002
Aconite Leaves....	0.25	Aconite Leaves ..	0.025	Aconite Leaves..	0.00625
Digitalis	1.0	Digitalis	0.1	Digitalis	0.025
Gelsemium	2.5	Gelsemium	0.375	Gelsemium	0.1
Squills Acetic	0.75	Squills Acetic ...	0.5	Veratrum	0.015
Strophanthus	0.025	Squills Alco.	0.25		
Veratrum	0.5	Strophanthus ...	0.0025		
		Veratrum	0.05		
		Convallaria	0.075		
		Apocynum	0.075		

(*b*) *Cats.—Hatcher and Brodie's Method.*—This method consists in determining the minimal fatal dose per kilogram of cat when the drug is injected

slowly into the femoral vein, the standard chosen for the digitalis group being the cat-unit.

Cat-unit.—The amount of crystalline ouabain which is fatal within about 90 minutes to a kilogram of cat when the drug is injected slowly and almost continuously into the femoral vein. A cat-unit is equal to almost precisely 0.1 mg. of crystalline ouabain, or one ten-millionth of the weight of the animal.

Apparatus Necessary for the Experiment.—Accurately graduated syringe or burette, cat-board, two graduated burettes. Operating instruments: scalpels, forceps, grooved director, hemostat, bulldog clamps, glass seeker, 2 small glass cannulas, and silk ligatures.

Animals.—Cats of medium size (1.5 to 4 kg.) in good physical condition.

Preparation of Experiment.—After weighing, the animal is completely anesthetized. This is best accomplished by one of the two following methods:—

1. *Ether Anesthesia.*—The animal is placed in an air-tight box or bell-jar, into which is dropped a sponge saturated with ether; the animal is allowed to remain until all voluntary movements cease. It is then removed from the box or jar and fastened upon the cat-board, the anesthetic now being given on cotton covered with a towel, care being taken to cover the whole mouth of the animal.

2. *Morphine Acetone-chloroform Anesthesia* (Edmunds and Cushny).—The animal is placed in a box 35 cm. long, 18 cm. wide, and 18 cm. deep. The box is furnished with a sliding lid. A V-shaped cut is made in the end of the lid and in the corresponding end of the box, so that the animal may be securely clamped in this opening, allowing the head to protrude. The lid is fixed with a nail and then 40 to 60 mg. of morphine are injected with a hypodermic syringe into the skin of the neck. This is followed by 0.3 cm. per kilogram of acetone-chloroform dissolved in alcohol administered by the stomach-tube. As soon as voluntary movements cease the cat is removed from the box and tied upon the board.

Next an incision two inches long is made over each saphenous vein at its junction with the femoral vein and the tissues severed just enough to free about one inch of each. A short cannula of small bore, with rubber connection, is then tied into each saphenous vein close to its junction with the femoral vein and the vein clamped off with a small artery clamp.

Preparation of Solutions.—Two solutions are required.—*First*, the standard solution, prepared by carefully dissolving 0.1 mg. of crystalline ouabain per kilogram body-weight of animal in a sufficient quantity of normal saline solution to render it possible to measure accurately aliquot portions of this dose.

Second, the preparation to be standardized, which should also be carefully diluted with normal saline solution. If a tincture or fluidextract, it should first be freed from part of the alcohol present by evaporation on a water bath.

Methods of Injecting.—Two glass syringes, or, better, graduated burettes, may be used for making the injections. One marked *A*, for the standard solution, is fastened to the rubber connection of the cannula in one saphenous vein,

while the other, marked *B*, for the solution to be standardized, is fastened to the cannula in the other vein.

Actual Standardization.[6]—"When crystalline ouabain, amorphous strophanthin, or a preparation of strophanthus is to be tested, it is only necessary to inject the solution from a syringe or burette into the femoral vein until the animal begins to show toxic symptoms. The injection is then interrupted, or continued more slowly until the unmistakable signs of approaching death are seen. These signs are so typical that one is rarely mistaken concerning them. They consist in irregularity of the heart, difficult respiration, convulsions, and frequently a peculiar cry, after which recovery is extremely rare. If death does not occur in a few minutes the injection is continued with extreme caution.

"Other members of the digitalis group may be tested in the same manner, but, as a rule, the results will be somewhat too high, and in that case the necessary correction, usually amounting to about 20 per cent., may be made, or the assay may be made more accurately by a modification of the technique.

"Somewhat more uniform results are obtained if about 75 per cent. of the total amount of the digitalis body is injected in the first 15 minutes and the remainder in the following hour. These results will still be too high, and we have therefore devised a modification of the method of estimating some of the other digitalis bodies which give results that we believe to be nearly as accurate as those obtained with crystalline ouabain itself.

"Just as the analytical chemist may find it desirable to determine the alkalinity of a liquid by adding an excess of acid and titrating back with an alkali, so we have here been able to obtain more accurate results in some cases when we inject a measured amount of the digitalis body (tincture or infusion of digitalis or digitoxin) in the first period of 10 minutes, and after an interval of 20 minutes continue the injection, substituting a solution of crystalline ouabain for that of the digitalis body under examination, until the death of the animal, or until toxic symptoms appear.

"The difference between the amount of crystalline ouabain actually used to complete the assay and the 0.1 mg. per kilogram of animal (the amount which would have been required in the absence of the digitalis body) represents the activity of the digitalis used.

"The following example will illustrate the mode of computing the activity of the digitalis body tested: A tincture representing 70 mg. of digitalis per kilogram of cat was injected into the femoral vein and after 20 minutes the injection of a solution of ouabain was begun. The animal died with the typical symptoms of digitalis poisoning when 0.0142 mg. of crystalline ouabain per kilogram had been injected. The difference between 0.0142 mg. and 0.1 mg. (which would have been required had the ouabain been used alone) is 0.085 mg., or 85.8 per cent., of a cat-unit; hence, 70 mg. of digitalis equals 85.8 per cent. of a cat-unit, and 81.6 mg. of the digitalis equals one cat-unit."

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6 Hatcher and Brodie method, Am. Jour. Pharm., p. 362, Aug., 1910.

(*c*) *Frogs.*—1. *Houghton's "12 Hour" Method.*—With this method the strength of the drug is determined by finding the minimum amount per gram body-weight necessary to cause the death of the animal within 12 hours.

Apparatus Necessary for Experiments.—One all-glass syringe or sharp-pointed pipette; frog-boards; forceps; scissors; scalpel, and a tank arranged for maintaining constant temperature.

Animals.—The frogs should be healthy, freshly caught, carefully handled, and kept in wet moss until they can be placed in tanks, with running water, in the laboratory. These storage tanks should be kept at a temperature of 10° to 15° C. This is a primary and important essential, as at the ordinary summer heat the frogs die *very* rapidly, while when kept at a temperature of from 10° to 15° C. death rarely occurs.

Another precaution in using frogs as assay animals is that the experiments should be carried out at the same temperature on account of the great susceptibility of the frog to heat. A temperature of about 20° C. is the best, because, being about ordinary room temperature, it can easily be maintained. This may best be accomplished at all seasons by means of a simple apparatus consisting of a large galvanized iron tank partly filled with water in which are placed the small cages containing the frogs. The temperature of the tank is raised or lowered by merely heating or cooling the water.

Since the dose is computed per gram of body-weight, frogs of any size may be used, but it is thought best to use those only of medium weight (20 to 35 Gm.) and of nearly uniform size, varying from one another not more than 5 Gm.

Any species may be employed, provided both the standard and the unknown preparation are tested upon the same species.

Preparation of Solution.—The preparation to be tested is diluted with a sufficient quantity of normal saline solution to make the doses injected measure about 0.5 c.c.

Method of Injecting.—The injections are made into the abdominal lymph-sac by means of an all-glass syringe or a sharp-pointed pipette.

Actual Standardization.—The general procedure is essentially the same as that given for Reed and Vanderkleed's guinea-pig method, differing only in the two following points: 1. The results are recorded at the end of 12 hours instead of 24 hours. 2. The minimum lethal dose is expressed in terms of grams per gram body-weight instead of in grams per 250 Gm. body-weight.

2. *Famulener and Lyons's "1 Hour" Method.*—This is considered by most workers to be the best of the frog methods. It consists in determining the minimum dose of the drug that will cause permanent systole of the frog's ventricle at the end of exactly one hour.

Apparatus Necessary for Experiment.—Same as under Houghton's "12 hour" method.

Animals.—In addition to the precautions given under Houghton's "12 hour" method, Famulener and Lyons have suggested that, since frogs are markedly influenced by external surroundings, temperature, season, relation of time of injection to time of feeding, etc., it is advisable to guard against the

possibility that the frogs used for any particular series of experiments might be above or below the average susceptibility by standardizing each lot before they are used for assay purposes. For this purpose most workers have adopted crystalline ouabain. When a new lot of frogs is received a test is made by injecting one frog with the standard "minimum dose" of ouabain, fixed by previous experiments, to another 10 per cent. more, and to a third 10 per cent. less, than the standard dose. If the result of this experiment shows that the frogs are not of normal susceptibility it is then necessary to determine the minimum dose for this particular lot of frogs and to correct all succeeding assays accordingly.

Preparation of Solutions.—The method of preparing the solutions for injection is the same as that given for Houghton's "12 hour" method, except that the authors of this method advise that in all cases care shall be taken that the solvent is of the same alcoholic strength, as a certain amount of alcohol is necessary, in many cases, to effect solution of the substance injected.

Method of Injecting.—The solution to be tested is accurately measured by means of an all-glass syringe or sharp-pointed pipette. The floor of the mouth under the tongue is then punctured and the contents of the syringe or pipette delivered directly into the anterior lymph-sac of the animal.

Actual Standardization.—Select and carefully weigh a series of four healthy frogs of approximately standard weight (40 Gm.). Inject them as described above with $^{9}/_{10}$, $^{10}/_{10}$, $^{11}/_{10}$, and $^{12}/_{10}$, respectively, of the standard dose of the preparation being tested for each 40 Gm. body-weight of animal. The animals are then placed in cages in the tank (previously regulated to maintain a temperature of 20° C.), and allowed to remain there for about 55 minutes. They are then removed, pithed (both brain and cord), tied to frog-boards, and the thorax laid open so as to expose the heart. If this is already completely paralyzed, the dose has been excessive; if the pulsation still continues, although at a diminished rate, the dose has been insufficient. Basing the dosage upon these results, other series are then injected with progressively increasing or decreasing doses, as the case may be, still further diminishing the variation between doses until the minimum amount of the drug, per 40 Gm. body-weight of animal, is found which will just cause paralysis of the heart's action in one hour.

The authors of this method designate their "minimum dose" as the smallest amount of the drug which, in one hour, will produce the following typical condition[7]:—

"The apex of the ventricle is paralyzed, but at the base (region of the auriculoventricular system) there is occasionally a very faint contraction, indicated only by a color wave which is noticed quite commonly to have its origin at the left base of the ventricle, passing thence across the ventricle, while the auricles are much distended but continue to pulsate regularly." The activity of the preparation tested is then computed between the "minimum dose" of the preparation tested and the "standard minimum dose" by simple proportion.

Some slight modifications of this method have been adopted by various

[7] Famulener and Lyons, Proceedings of the Amer. Pharm. Assoc., p. 417, 1902.

workers with the idea of securing greater accuracy,—the most important of which are: First, that the assays should all be carried out at constant temperature. Second, that the "minimum dose" should be the smallest amount of the drug which, in one hour, will produce the following condition: The heart is paralyzed, but when stimulated by touching it with the end of a pair of forceps or scissors it will respond with an additional contraction. If the heart will not give this "contraction on stimulation" the dose has been excessive; if it still pulsates the dose has been insufficient.

3. *Focke's Method.*—With this method the heart is exposed *before* the injection of the drug. The strength of the preparation "V" is determined by means of a formula in which the weight of the frog is divided by the dose multiplied by the time, in minutes, required to complete the reaction.

Apparatus Necessary for Experiment.—Same as under Houghton's "12 hour" method.

Animals.—Frogs in good physical condition, which have been in captivity not less than three days and weigh between 25 and 30 Gm. They are not to be collected before the end of June and should be kept in tanks supplied with water.

Preparation of Experiment.—Six hours before carrying out the actual standardization several frogs of about standard weight (25 to 30 Gm.) should be removed from the tank and placed in jars in the laboratory and kept at a temperature not exceeding 17° C.

Preparation of Solutions.—The solution to be injected is prepared by making a 10 per cent. infusion of the drug.

Method of Injecting.—The injections are made by means of an all-glass syringe or sharp-pointed pipette into the two leg lymph-sacs.

Actual Standardization.—An unpithed frog is fastened to the board and the heart carefully exposed in the usual manner without causing any loss of blood; 0.25 c.c. to 0.35 c.c. (about one-fortieth of the weight of the frog) of the infusion is then injected into the lymph-sac of each leg. The heart is then watched and the time required to cause systolic stoppage is noted. This is usually from 7 to 15 minutes. If the heart stops in less than 7 minutes, the dose has been too large, while if it continues to pulsate after 20 minutes it has been too small.

Basing the dosage upon the result of this primary experiment, other frogs are injected with larger or smaller doses, as the case may be, until four are found in which the heart has stopped between 7 and 15 minutes. The frogs are then pithed and weighed.

The toxic value of the preparation (V) is then determined by means of the formula $V = \frac{P}{d \times t}$, in which (P) represents the weight of the frog, (d) the amount of the drug injected, and (t) the time in minutes required to complete the reaction.

The relative strength of the preparation tested may then be expressed in percentage by comparing the (V) as determined by the experiment with the standard (V) adopted for that particular drug.

Focke states that the most concordant results are obtained if the experiments are carried out during the months of July, August, and September, but that accurate results for standardization purposes may be obtained at any season of the year if the animals are previously standardized and all subsequent assays corrected accordingly.

2. Blood-pressure Method.—*Apparatus Necessary for Experiment; Animals; Preparation of Experiment; Method of Injecting.*—Same as given under standardization of epinephrin.

Preparation of Solution.—All preparations to be tested should be diluted with normal saline solution to tincture strength, tinctures and fluidextracts first being freed from the greater part of alcohol by evaporation on a water bath.

Actual Standardization.—The blood-pressure tracing is started on a slowly revolving drum. After obtaining a tracing of normal pressure several inches in length the drum is stopped and 1 c.c. of the preparation to be tested is injected into the femoral vein. Another similar injection is given, after allowing from 1½ to 2 hours to elapse, in order that the effects of the previous injection may partially pass away. As the action of this class of drugs is prolonged and cumulative, more than two injections should never be given to the same animal, because the first injection always modifies the succeeding injections. Three or four dogs should be used and the average percentage rise of blood-pressure taken as the figure of potency.

The immediate rise produced by subtoxic doses is never marked, in many cases being so slight that a variation of 15 or even 20 per cent. in the size of the dose injected produces no measurable difference in the resultant rise. This method is, therefore, useful only for *roughly* determining the quantitative activity of a preparation, and does not give results sufficiently accurate to permit its being used for standardization purposes.

Standardization of Small-pox Vaccine.

It will be readily seen that the standardization of small-pox vaccine cannot be accomplished in the same way nor does it mean the same thing as the standardization of other biological products such as diphtheria antitoxin, tetanus antitoxin, and the various bacterial vaccines. The reason for this will be obvious when we recall that we have no means of isolating the active principle of small-pox vaccine; nor, in fact, has the specific agent been absolutely determined. Two points, however, are to be borne in mind in discussing this problem:—

1. The potency of the virus.
2. Its purity.

POTENCY.

The potency is determined by various methods in different institutions. All these methods depend, however, on the production of the specific lesion in some susceptible animal. Our method is to use the calf as the determining factor. A sample of the vaccine to be tested is inoculated in linear incisions about four inches long and the virus rubbed in on the scarified surface. The

incisions are about one inch apart, each representing a sample of a virus. The calf remains in the incubating stable for about six days, just as in the ordinary procedure of vaccine productions. At the end of that time an inspection is made and the material used in each test graded, thus: "A," "B," "C," "D," "E," "F," and "G." No virus is allowed to issue from the laboratory which does not grade at least "C" on the last test.

PURITY.

The active principle of vaccine virus apparently develops in the epithelial cell. The time required for cultivation on the calf is from four to six days. Germs from external sources may therefore come into direct contact with the vesicle, their number and character depending somewhat on the surroundings. The skin, moreover, appears to be the normal habitat for certain cocci and occasionally other bacteria as well. Virus growing in the skin of the animal for six days is thus open to these two sources of infection. Contaminations of this character were called by Copeman "extraneous organisms," meaning that they have nothing to do with the production of the specific disease known as "cow-pox," though they may or may not affect the character of the vesicle. It is naturally important that we should determine whether these organisms are pathogenic or not. The following method is employed for this purpose:—

A sample of the vaccine is tested aërobically by the usual plate-culture method and the number and character of the germs noted. Samples of any bacterium which may be pathogenic to animals are isolated and tested. No virus is allowed to issue until pathogenic germs are eliminated.

Anaërobe Tests.—As is well known, some years ago several deaths were reported from tetanus following vaccination. Since that time careful and elaborate tests have been made on all vaccine issued, to insure the absence of this germ, but up to the present none has been found by any of the laboratory investigators in the United States. Careful routine testing for this organism is, however, of extreme importance.

Different methods are used by the various laboratories, but all depend upon two factors:—

1. A microscopic examination for a round "end-spore" bacillus, growing anaërobically.

2. Examination for the presence of a powerful toxin produced by this germ, as determined by injection in various susceptible animals.

The test is made in the following manner: 10 c.c. of each batch of virus is grown in appropriate culture media under anaërobic conditions for ten days or longer, when a microscopic examination is made. Whether the characteristic bacillus is found or not, the culture is filtered, 5 c.c. of the filtrate inoculated into a guinea-pig subcutaneously, and the animal held under observation for ten days or longer.

Control Test.—In addition to the tests already noted, a given quantity of glycerinated virus is directly inoculated into an animal, which is kept under observation for one week or longer. This test is intended as a control.

All of these tests are duplicated by another department working independ-

ently, and the results must tally before a given batch of virus is allowed to issue.

STORING OF VIRUS.

After the virus has been prepared and tested by the methods above noted, it is stored at from 8° to 12° C. Investigations made at this laboratory some eight to ten years ago proved that virus could be kept indefinitely provided it be stored at at least 8° C.

For this reason the virus is made in winter, when the weather is most favorable for its production. It is then put in the cold at the temperature noted and can be drawn on even during the hot weather.

This was recently exemplified during the epidemic in Pittsburgh, when over 270,000 doses of vaccine were forwarded in one week, which would have been impossible under the present complicated methods of testing without cold-storage facilities.

Two points need to be emphasized in this connection: (1) Virus is quickly killed by even a short exposure to summer heat; so that as little as possible should be held in stock in drug-stores during that season, and, where possible, fresh material direct from the laboratory used. (2) Vaccine cannot be stored *too cold*, and should at least be kept directly on the ice, as being the coldest place obtainable.

DATING OF VACCINE.

Virus is dated in order to comply with government requirements. A moment's thought will convince anyone that this is largely arbitrary, and that perfectly active virus may be "out of date," while, on the other hand, virus may become absolutely inactive because of exposure to unfavorable conditions, with a large time margin left. The only safe method to pursue is to use the vaccine as soon after it is issued from the laboratory as possible, particularly in hot weather.

EFFECTS OF HEAT ON VACCINE.

In order to emphasize what has just been said, attention is called to the following chart, which shows the life of vaccine at different temperatures:—

Degrees Centigrade.	Degrees Fahrenheit.	Duration of Exposure.	Result.
60	140	5 minutes	Killed.
55	132	5 minutes	Weakened.
37	98	3 to 4 days	Killed.
21	70	1 to 3 weeks	Weakened.
10	50	3 to 6 months	Active.
—12	10	4 years	Active.

METHODS OF VACCINATION.

Two points require emphasis in this connection:—

1. *The Depth of Scarification.*—Various operators have suggested different methods, such as the puncture, linear incisions, scarification, and the hypodermic method, but in the use of any of these methods care should be taken only to pierce the epidermis. *Draw no blood.*

2. *The size of the scarifications* is emphasized, particularly abroad, it being claimed by the Local Government Board of England that one-half square inch is necessary to give full protection. This is usually accomplished in England by four insertions. In this country one scarification is usually considered sufficient, but it often happens that the physician covers more than one-half square inch in making it.

SUBSEQUENT CARE OF THE VACCINATION SITE.

Attention has already been called to the fact that tetanus occasionally follows vaccination. It also sometimes happens that infection follows owing to carelessness or the presence of dirt, or to breaking into the vesicle through some accident. Should this latter happen, infection might easily result, and in fact a number of cases investigated seemed to show that the tetanus organisms had entered in this way. We would therefore specially call attention to the fact that the vaccination site should be protected by some means from external contamination. If a shield is used it should be frequently removed and the surface beneath cleaned. The shield should not press on the inflamed area.

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DISCUSSION.

Dr. Oliver T. Osborne, of New Haven, Conn., said that he had watched Dr. Stewart's efforts with the greatest interest. They were certainly needed, for the general opinion among physicians seemed to be, that all that was necessary was to

write out a prescription, and the Lord would do the rest. Now that we saw something of what Dr. Stewart had done, we should fight in company with him. He himself was a member of the Committee on Scope in the preparation of the next issue of the United States Pharmacopeia, and this committee had fixed upon, without discussion, a very few drugs for admission to it—not more than 12. But, by the time that the work had got through all the various other committees, it would be found that the new Pharmacopeia would contain, as heretofore, a quantity of perfectly useless drugs, mostly at the instance of pharmaceutists who urged that some physicians continued to order them. If one desired to prescribe tincture of saffron, for instance, why could he not go back to some issue of the U. S. P. in which it was official? Our Pharmacopeia was the most antiquated medical book in the world—purely medieval. As instances of its medieval character might be mentioned the compound cathartic pill, of which the surgeons were so fond, and the good old-fashioned brown mixture. In spite of all this, Dr. Stewart's efforts would finally triumph, and his work would be manifest in future Pharmacopeias.

Dr. Charles E. de M. Sajous, of Philadelphia, said that at the annual banquet he had emphasized the need of courage and perseverance, regardless of criticism and opposition, in pursuing original lines of research or thought which one believed to be of value to human welfare. This applied to the class of work in which Dr. Stewart had so long been engaged. For thirty years he had patiently emphasized the importance of drug standardization and the profession had been gradually learning to appreciate the practical value of carefully standardized drugs. Nothing would so paralyze our efforts as to have to fight disease with impotent or inferior weapons. Last winter in the course of work on the standardization of tincture of digitalis in Dr. Sajous's laboratory it was found necessary, on account of deterioration, either to increase the dosage at very short intervals or to obtain fresh tincture. To devise the best means to ascertain the actual value of all drugs subject to change would alone afford the physician the possibility of giving serious aid by judicious employment of these drugs. It was a humane work therefore in which Dr. Stewart was engaged, and the speaker hoped that the Society would give Dr. Stewart all the encouragement and assistance in its power.

P. S. Pittenger, Phar. D., of Philadelphia, said that, in addition to what Dr. Stewart had stated as to the necessity of standardization, he wished to present a very convincing table showing the variation in physiologic activity, *before standardization*, of some U. S. P. preparations assayed during the past year in their laboratory. Everyone present had no doubt either seen or heard of the wide variation in the activity of unstandardized galenical preparations and in the crude drugs themselves. He found, however, that most physicians did not realize the wide range of this variation, and therefore thought the members of the Society would be interested in hearing some *actual laboratory results* upon the subject:—

Drug.	Number of samples assayed.	Variation (percentage).
Digitalis tincture	51	30 to 444
Digitalis fluidextract	16	26 to 160
Digitalis solid extract	7	29 to 100
Ergot fluidextract	17	0 to 310
Aconite leaves tincture	6	38 to 111
Aconite root tincture	12	33 to 363
Aconite root fluidextract	7	52 to 266
Aconite root solid extract	10	6 to 166
Aconite root powdered extract	11	5 to 100
Cannabis indica fluidextract	15	40 to 150
Cannabis indica solid extract	4	71 to 125
Gelsemium tincture	7	64 to 156
Gelsemium fluidextract	7	65 to 220
Gelsemium powdered extract	3	88 to 187
Strophanthus tincture	12	55 to 277
Squill fluidextract	13	71 to 153

Supplementing Dr. Sajous's remarks on the rapid deterioration of digitalis preparations, he would like to announce, before publication, the condensed results of one of his recent investigations into the subject of ergot deterioration. This was an exceedingly important consideration for the therapeutist, for, as Dr. Vanderkleed had said in his section on Chemical Standardization, "Of what use is standardization to the physician if the carefully adjusted preparation shall have lost part or all of its activity before it is placed in his hands for use? Fortunately, only a few drugs and their preparations are subject to rapid deterioration. While no preparation should be looked upon as permanent, and freshness is always desired, the preparations of most of the alkaloidal drugs are quite stable and fluidextracts of such drugs as belladonna, nux vomica, cinchona, ipecac, and opium will remain potent and reliable for years, if kept tightly stoppered in a cool place. On the other hand, digitalis, strophanthus, and ergot preparations, *particularly the latter*, deteriorate quite rapidly under the ordinary conditions under which galenical preparations are kept." In the case of ergot the activity became greatly impaired in many instances in from two to three months. As all know, the subject of ergot had for a long time occupied the minds and attention of various workers, but until the present time no one had succeeded in devising a method by which manufacturers of preparations of ergot could put this product on the market in a form which would remain stable for a definite time. Most of the workers had claimed that, when tightly corked, preparations of this drug had been found to retain their original activity much longer than when loosely corked. This fact led him to believe that *air* must be the cause of this deterioration. Ordinarily, the evaporation of the menstruum would tend to increase rather than decrease the strength of a preparation. Accordingly, a little over a year ago he had started an experiment with ergot in order to prove the truth of his theory that *air* was the principal cause of deterioration:—

First, he secured a sample of fluidextract of ergot and tested it physiologically, finding that when injected into dogs in doses of 0.08 c.c. per kilo it produced an average rise in blood-pressure (from 5 injections, into several animals) of 45 mm. This was then divided into four portions, which were kept for one year in the laboratory in the following manner: The first portion was put up under vacuum in tubes specially designed and made by him for this purpose. The second portion was filled into bottles which were tightly corked and remained for one year unopened. The third portion was filled into bottles which were kept loosely corked for one year. The fourth portion was tightly corked, but opened occasionally throughout the year. After three months a test was made of the fourth portion (opened occasionally), which showed a deterioration of 37 per cent., producing only a 30-mm. rise in blood-pressure, instead of 45 mm., as when originally tested. A second test was made of this portion at the end of nine months, when it was found to possess only 42 per cent. of the original activity, *i.e.*, to show a deterioration of 58 per cent. It produced a rise in blood-pressure of only 20 mm. instead of the 45 mm., as when originally tested. At the end of a year all four portions were tested, with the following results:—

How kept.	Number of injections.	Average rise of blood-pressure.	Average fall of blood-pressure.
In vacuum	9	49.1 mm.	8.7 mm.
Tightly corked	5	29.8 mm.	12.0 mm.
Loosely corked	4	16.5 mm.	34.5 mm.
Tightly corked, opened occasionally	3	15.0 mm.	40.0 mm.

The chemical assay gave the following results:—

How kept.	Date tested.	Results.
Original sample	5—6—11	0.163% total alk.
In vacuum	5—6—12	0.168% total alk.
Opened occasionally	5—6—12	0.076% total alk.

It could thus be seen that by adopting the vacuum method of putting up ergot the rate of deterioration can so be retarded as to make this product one of stable quality for at least a definite time. This method would make it possible not only to supply the physician with a preparation which would maintain its "standard strength," but also enabled the experimenter to preserve a standard preparation with which he could compare the strength of new lots of drug and their preparations, and thus adjust them to "standard strength."

Dr. Sajous said he had found that he could preserve his liquid adrenal preparations very well by keeping them covered with a layer of oil, to prevent oxidation; otherwise their tendency was to change color and become inert. He remarked that every plant resembled our blood, *i.e.*, that its fluid contained an organic ferment which, acting as a catalyzer, had the ability to absorb oxygen and to sustain metabolism in the plant cells by surrendering its oxygen to them.

Dr. Francis M. Pottenger, of Los Angeles, Cal., said it would appear that at last we were getting some light on this subject. It seemed to him that if we could get a dozen or two drugs on a really scientific basis it would be a great gain. This, however, could be accomplished only by continued specialized work. For fifteen years he had been working on tuberculin, but many of the preparations of this he had not attempted to try. He had been content to perfect himself in the use of some half a dozen tuberculins, and he now knew just what each of these could do. In regard to digitalis, he had been interested in Mackenzie's work, and in the report of a recent lecture by him he had noted that this authority said: "Use digitalis and push it till you get its physiological effects." This he had followed with varying dosage, but good results. It would not do for us to be mere machines. We must individualize and study each case separately, as had been so well brought out in the discussion on diabetes. Therapeutics would take a better position if more attention were paid to the physiologic action of remedial agents, and it devolved on us to do all that we could to place this branch of medicine on as firm a basis as possible.

Dr. H. Beaumont Small, of Ottawa, said it was to be regretted that, while all felt so strongly on this matter, nothing practical had been done by the Society to assist in materializing Dr. Stewart's ideas. He would, therefore, suggest that the subject be referred to the Council, with the request that it bring it to the attention of the U. S. P. revision authorities and of the American Pharmaceutical Association.

A motion was made that Dr. Stewart's paper be so referred. An amendment was offered to the effect that it should be referred to the Committee on Therapeutic Research, which should confer with Dr. Stewart as to the best steps to be taken, and this was unanimously carried.

Dr. Stewart, in closing, expressed his grateful appreciation of the handsome endorsement which the members of the Society had given his efforts. One thing had been lost sight of, and that was that such work must be done under commercial auspices, for the problems involved in drug standardization were commercial as well as professional. Furthermore, the great commercial houses engaged in the pharmacal and chemical industries were in a better position to promote original materia-medica research than educational institutions or even government laboratories, because their operations are conducted on a large scale. And the experience of their experts, owing to their large operations, was correspondingly extensive; consequently they were in a position to speak with greater authority. The commercial interests, however, should not be permitted unlimited power in the matter, but should be carefully held in check by the professional societies. To accomplish this the experts connected with the scientific departments of these houses should be invited to fellowship, and through them the houses be held accountable. In this way the societies could avail themselves of the great facilities of the houses and their experts without danger of commercial exploitation.

THE THERAPEUTICS OF SACROILIAC RELAXATION AFTER OPERATION, LABOR, ETC.

By A. ERNEST GALLANT, M.D.,

Consulting Surgeon, Jamaica Hospital, New York, and Eastern Long Island Hospital, Greenport, N. Y.; Surgeon, Baptist Deaconess Home and Training School, New York, etc.,

NEW YORK, N. Y.

While surgeons of the nineteenth century were more or less familiar with diseases of the sacroiliac joints, and obstetricians recognized the presence of relaxation of the iliac synchondroses and the pubic symphysis during pregnancy, parturition, and the puerperium, disorder in this locality remained but little sought for until the appearance of the excellent paper of Goldthwaite and Osgood,[1] wherein were detailed the results of a most careful study of the sacroiliac synchondrosis, and the fact demonstrated that this is a true joint, subject to luxation and dislocation, and the source of symptoms variously and improperly designated as lumbago, rheumatism, sciatica, etc., occurring after injury, operation in the lithotomy posture, labor, prolonged confinement in bed, lifting from the floor, etc.

From a remarkable series of experiments on bodies shortly after death, these authors demonstrated that "A great arc of motion exists and the joint (sacroiliac) can be readily dislocated. . . . . Naturally when this dislocation could be so easily performed in the anatomical specimen the same motion could take place in the living subject when the ligaments were not in tone." and be brought about by "the same factors which would cause relaxation or sprain of ligaments in any part of the body."

Etiological Classification.—The causes of sacroiliac disorder have been classified as follows[2]:—

I. *Physiological*:—

(*a*) Pregnancy; (*b*) parturition; (*c*) menstruation; (*d*) general lack of tone.

II. *Traumatic*:—

(*a*) Acute: 1. Direct blow on sacral region.

2. Twisting backward in falling, or sudden twist or wrenching; stumble; sitting on a chair not there.

3. Strains due to lifting heavy objects,—the so-called "stitch in the back"; lithotomy position.

[1] Boston Med. and Surg. Jour., 1905, clii, 593, and Jour. Amer. Med. Assoc., 1907, xlix, 768.

[2] Dunlop: N. Y. Med. Jour., 1906, lxxxiv, 1131-1134.

(*b*) Chronic: 1. Relaxation of the lumbar curve of the spine, due to long recumbency, *e.g.*, in typhoid, fractures, etc.

2. Body malformations causing prominent, pendulous abdomen: obesity, tumors, enteroptosis.

3. Faulty methods of dress: corsets, shoes.

4. Occupations and attitudes.

III. *Diseases:*—

(*a*) Infectious arthritis.

(*b*) Hypertrophic arthritis (osteoarthritis).

(*c*) Atrophic arthritis (rheumatoid arthritis).

Symptoms.—As has been noted by different observers, there is a great similarity in the symptomatology of this class of cases, though the symptoms vary in degree and constancy.

1. *Backache* involving the sacral and lumbar regions, causing but moderate discomfort in some, lumbago-like stiffness in others, and most intense muscular spasm which causes the patient to scream with every motion.

2. *Pain*, radiating from the gluteals down the thigh to the calf (and consequent disability) may either be present only to a moderate degree, as if due to a so-called "backstrain," or, in others, be of a severe lancinating character which wholly incapacitates the patient.

3. *Occipital headache* is said to be present in some cases, and cured by immobilization.

4. *Disability.*—When the patient is attempting to walk, the back is held rigid, and at a greater or less angle forward; she steps in the most cautious way, with a somewhat waddling gait, as if seeking to avoid any jarring or a misstep.

Bending forward or backward is very greatly limited by lumbar spasm. In lateral bending, motion is limited away from the affected side, and restrained at the point of pain.

In bed the patient finds it very difficult to secure a comfortable position. She cannot lie on the back or affected side, cannot sit up or lie down, without pain; in fact, any motion aggravates her suffering. For some only does the semireclining posture afford any relief, by night or day.

Physical Signs.—*Inspection* of the joint area may show no perceptible deviation from the normal; in other instances there may be (*a*) lateral curvature of the spine, or (*b*) obliteration of the spinal curve: (*c*) the pelvis may be tilted to the same side, the posterior superior spine being elevated; (*d*) the back may be flattened; (*e*) the sacrum may be more prominent.

Diagnostic Palpation and Manipulation.

Patient standing: (*a*) Deep pressure over the joints elicits tenderness or pain.

(*b*) Mobility may be demonstrated:—

1. By anteroposterior pressure with one hand on the symphysis pubis and the other on the joint.

2. By lateral compression of the iliac crests while actively or passively lifting the leg with the knee bent, causing lumbar pain.

Patient lying face down:—

(*a*) Hyperextension—Lift extended limb: motion limited; sharp, stinging pain in joint.

(*b*) Rotation—Rotate limb: pain in joint with spasm on flexion, abduction, or adduction.

(*c*) Place one finger on the sacrum, another on the posterior superior spine: motion of joint easily felt.

Pelvic palpation in relaxation would show nothing. In dislocation it would be very painful and at times hard to make, though mobility might be determined by grasping the sacrum between the fingers in the vagina and the thumb on the sacrum, and rocking it backward and forward.

When the bone is diseased, swelling and tenderness can be recognized on pelvic palpation.

Reduction and Fixation.—The correction of sacroiliac subluxation, according to Goldthwaite,[3] is performed as follows:—

1. Simple hyperextension of the spine by a firm pillow "under the hollow of the back" may, by raising the lumbar spine, draw the sacrum into place.

2. Place the patient face down, with the thighs and legs resting on one table, the head and shoulders upon another, and the body hanging unsupported between.

3. Suspension or hyperextension of the spine.

4. Replacement under ether.

Meisenbach[4] reduces the dislocation by hyperabduction, hyperextension, and pressure on the sacrum, and recognizes that he has accomplished his object by a snapping which can be heard as the joint slips into place.

Differential Diagnosis.—The most striking diagnostic features are: (*a*) that drugs exert but little effect in allaying the pain and wholly fail to cure the disorder; (*b*) that fixation of the joints in relaxation, and after reduction, when dislocation is present, gives almost immediate relief.

Lumbago.—The pain is limited to the lumbar muscles, and readily responds to drugs, heat, and massage. If not, one must look for evidences of sacroiliac luxation.

Sciatica.—Goldthwaite is inclined to believe that nearly every case of sciatica is due to compression of the nerve cord by the mobile joint, and this we have found to be true in most of our cases.

"*True sacral disease* can be determined by the X-ray, stereoscopic views being the most satisfactory."[5]

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[3] *Loc. cit.*

[4] Meisenbach: Surg., Gynec., and Obstet., May, 1911.

[5] *Loc. cit.*

In an extremely interesting paper on "An Experimental Study of Certain Phases of Chronic Backache," Reynolds and Lovett[6] come to the conclusion "that static backache is essentially a mechanical disorder; that it is the result of a loss of balance producing local strain on the tissues in the lumbosacral region and elsewhere on the tissues in the posterior musculature. We further believe, and regard it as our most essential point, that, whatever the local mechanism which produces the symptoms may be, such backache is in a large proportion of all cases not a disease in itself (as suggested by such terms as 'hysterical spine,' 'relaxation of the sacroiliac joints,' etc.), but is a mere symptom-complex due to an abnormal attitude induced by peculiarities of the skeleton, lack of proper muscular balance, or abnormal conditions in the abdomen or elsewhere. We believe that in diagnosis the local condition should be regarded as primary only after every cause elsewhere has been excluded."

Pelvic diseases and menstrual disorders must be eliminated or receive appropriate treatment.

When to the more or less physiological relaxation of the synchondroses during menstruation is added dysmenorrhea, menorrhagia, or metrorrhagia due to cervical obstruction[7] the unfortunate patient is often compelled to go to bed for one or more days and helplessly endure.

Shortened, thickened, tense and tender uterosacral ligaments, holding the uterus in fixation, cause sacral pain, referred accurately to the synchondroses, when laughing, sobbing, sneezing, coughing, or on making any expulsive or lifting effort, whereby the uterus is forced downward and drags on the ligaments. Failure to recognize the full significance of this condition—which is very common—is apt to lead to a wrong diagnosis of sacroiliac relaxation or *vice versâ*.

Obscure Conditions.—By those who carefully digest the magnificent work of Goldthwaite and Osgood, Dunlap and Meisenbach, Albee, and others, and practise careful examination, exact differentiation, and appropriate mechanical treatment of sacroiliac relaxation and dislocation, such indefinite appellations as muscular rheumatism, neurasthenic or functional spine, chronic sciatica, and typhoid spine will be relegated to the limbo of medical misnomers.

The following cases are offered as illustrating a few of the varieties of sacroiliac relaxation. Many have been unconsciously cured, as it is my habit to put the kidney corset on all patients after operation, whereby the unrecognized relaxation has been overcome. Plaster strapping, half round the body, after operation no doubt plays an important part, by dragging on the ilia, and drawing the iliosacral joints apart:—

Case I.—*Antepartum fracture of ossified symphysis pubis and luxation of sacroiliac joints; relieved by strapping; cure by corset.* My attention was actively directed in 1905 to the pelvic joints by the suffering of Mrs. C3, aged 29, who during the last two weeks of pregnancy complained most bitterly of sacral and pubic pain, which prevented her from walking, sitting, or lying with comfort, except in the semireclining position, and was exaggerated by any motion involving a change of posture. The real

[6] Jour. Amer. Med. Assoc., 1910, liv, 1033-43.

[7] Medical Record, April 16, 1910.

condition was not appreciated until on Jan. 12, 1907, during delivery of the child by high forceps, crepitation was felt to originate from the symphysis pubis, which had evidently ossified and fractured during the last weeks of pregnancy. The same pain in the sacrum and bladder was complained of as before labor, with excruciating paroxysms on motion. The pain was completely relieved by strapping the pelvis very securely with adhesive plaster. Twelve days later she complained of gas-like pain along the right ureter and kidney region, the latter being palpable just below the chondral border, and easily replaceable when the pain ceased. She sat up in a chair the next day, and the joints gave no further trouble until the following March, when she had a fall. She came to see me the latter part of April, having noticed a movable lump on the left side (the left kidney); soreness at the end of the spine when in bed; looseness of the bowels; cramps; cold feet, and loss of weight. The left kidney was swinging, pendulum-like, toward the umbilicus. These symptoms all subsided on wearing a properly fitted corset, which she has used ever since.

As might be expected, in the writer's practice, relaxation of the sacroiliac joints has been most frequently met with in women after operation, and, in keeping with the observation of Goldthwaite, especially after the lithotomy posture and subsequent recumbency on a woven-wire mattress. This can be accounted for from the way the buttocks sink in the middle of the mattress; the sides fold up around the hips, compressing the ilia forward and inward, and stretching the ligaments over the joints. When the patient gets up she complains bitterly of sacral weakness and pain down the hips and calf of one or both sides.

Case II.—*Sacroiliac relaxation prior to operation; subsequent aggravation; cure by corset.* Mary B114 applied July 18, 1911, for relief from pain in the back, running down the hip, most severe in the "sinews" of the legs, and intermittent. She had first noticed the pain two years before, upon lifting a trunk. She also noticed a movable lump in the left side. On examination the lump proved to be the enlarged, fibroid uterus, extending on the left side up to the umbilicus, and which was believed to cause the pain by pressure on the pelvic nerve trunks.

Operation September 19, 1912. Supravaginal hysterectomy and enucleation of broad ligament cyst on the left; hemorrhoids removed. Left Deaconess Home Oct. 1st.

Oct. 9th, starting out for a walk, she was taken with a sharp pain, the same as that before operation, and had to go home. She could not sit, stand straight, or lie down, except in the semireclining posture. She returned to the Home and a movable kidney was found three inches below the chondral border. The foot of the bed was elevated. Pleurisy on the right side ran a severe course, but subsided on the seventh day, and she returned home on the fourteenth day.

Jan. 15, 1912, the patient came to the office, saying that the old pain had returned and was as bad as before the operation. It prevented her from working. Examination showed sacroiliac relaxation. The pelvis was fixed by plaster strapping and relief was immediately experienced. March 19th, a special corset was put on and she has been working ever since, though there was still some dull aching in the "sinews" when she was seen a month later.

Case III.—*Bilateral sacroiliac relaxation after operation; cure by corset.* Mrs. M100. Operated in lithotomy posture on Nov. 2, 1912, for cervical obstruction, with dysmenorrhea and backache. Dilatation and suture of a fenestrated drain into the cervix. Dec. 26th, severe backache and metrorrhagia. A Hodge pessary was inserted, but it gave no relief from the pain involving the whole left hip and cramps running down the right leg nearly to the foot. She could not lie on the left side. A pillow under the back gave no relief. Feb. 6th, examination developed pain on hyperextension and rotation; pressure over the sacroiliac joints was painful. Most severe pain induced

when she tried to touch the floor with the fingers while the knees were held stiff. Bed making caused very intense pain. Plaster strapping gave immediate relief. March 3d, special corset put on. May 10th, she reports that she is very much better, but *cannot get along without the corset.* The left hip still hurts at night only, when the corset is removed. Advised to wear a heavy muslin binder at night.

CASE IV.—*Sacroiliac relaxation while in bed for movable kidney; jaundice; recurrence.* Miss W36 came under my care in July, 1906, with nausea, vomiting, pain in the right loin (Dietl's crises), and deeply stained, yellow skin. Drugs failing to give relief after five days, she was put in bed and the right kidney found prolapsed two inches. The foot of the bed was raised ten inches; the crises ceased and the jaundice rapidly subsided. July 18th, on getting out of bed, she experienced great sacral pain on walking, with dysuria, which was relieved when she was fitted with a specially made corset.

January 28, 1912, the patient wrote: "I have been practically laid up with a bad back for three months. It came very suddenly. Was so stiff I could not comb my hair, or button my shoes, or get up or sit down without making several attempts. The pain was across the lower part of my spine, half-way between my waist line and end of spine. The extreme stiffness and pain lasted about ten days and then I limbered up a bit; but the pain is still there and at times the stiffness returns, but not so bad as at first. I have tried all the lumbago and rheumatism cures I ever heard of, to no avail. Have baked myself for days, and dieted, have not touched coffee, tea, 'booze,' or red meat for weeks, and still have the pain. Have not consulted any 'M.D.' (Patient a doctor's daughter.) I also have a pain up my right side, under my ribs;—sort of a swollen pain, if you know what that kind of a pain feels like. Do you suppose that my kidney has kicked loose again? or has my liver slipped its cog this time? Probably a corset might help. Am getting desperate, dragging around half-dead; can't sleep at night, and am getting so irritable and nervous. I eat nails."

The patient made a corset for herself and has had no trouble from the sacroiliac joints or the movable kidney since. She has regained her health, weight, and better disposition.

Since 1907 we have been consulted by five men suffering from the "sciatic" type of sacroiliac relaxation, one simulating lumbago, the others with pains referred to the joint, the thighs, back and calf muscles. Here is what one wrote of his own experience:—

CASE V.—*Sacroiliac relaxation simulating sciatica, of thirty-three years' duration.* "Feb. 6, 1912. I am 52 years of age and have been a victim of 'sciatica' since I was 19 years old. It developed while I was a student at college and became so troublesome that a year later I consulted one of the leading surgeons in New York City. He concluded there was forming or had formed around the hip-joint some kind of a growth (adhesions) which could be destroyed by violently bending or flexing the joint, and this he did, giving me ether for the operation. The resulting soreness did not wear away for many months and I had no relief from the old trouble. Some five years later I was dosed with medicines for six months under the theory that there was a dryness in the hip-joint, and that it could be relieved by medicines. It was some two years before this dosing that I was cauterized with a hot iron, and afterward took a long course of hot baths and underwent considerable massaging. In my tenth or twelfth 'sciatic' year I began to try stretching the nerve by lying on my back and drawing the legs in straight position over the body and this after many weeks' trial seemed to have some good effect. This nerve has, however, through all these years given me more or less pain, and has kept me constantly aware of the fact that I have at least one sciatic, viz., the left one. It is quite sensitive, and, as a rule, a slight misstep with the left leg will produce a sharp pain lasting for some minutes.

"The most acute attack that I recall was one lasting five or six weeks in February and March, 1910, when you treated me.

"At times when walking there is a 'crackling' noise in or near the hip-joint. It sounds and feels as though there was an uneven place in the joint, at each step." Signed "W. F."

After exhausting all his former remedies, internal and external, Mr. F. came under my care and I, failing to recognize the true condition, wasted considerable time drugging, rolling the nerve, vibrating, blistering, etc., and finally did what should have been done at first,—encircled the pelvis with plaster straps,—with the result that in a few days he was out. After the plaster worked loose he discarded it, and has had no severe pain since.

The condition in this case may well be contrasted with the acute attack of real sciatica with which my father was for some weeks a sufferer, but which was cured by forcibly rolling the nerve, at its exit from the pelvis, under the thumbs for three *séances*. The trouble has not returned during the past nineteen years.

Treatment.—As might be expected, neither drugs, diet, nor local applications will avail in relaxation or dislocation of the sacroiliac synchondroses. Immobilization in the former case, reduction and fixation in the latter, must be instituted.

In relaxation we have always succeeded in securing almost immediate relief by encircling the pelvis on a level with the anterior superior spines with adhesive plaster, the ends being lapped over the sacrum and secured from slipping by a safety pin passed through both layers of plaster. Later this can be replaced by a strong inelastic belt for men or our special corset for women.

While in our hands plaster strapping has proved efficient for temporary immobilization, other clinicians have in some cases deemed it necessary to apply a plaster-of-Paris jacket or steel brace, and follow this up by a belt worn for some months, until the joint is restored to its natural, relative immobility.

While differing from most observers as to cause and effect, Reynolds and Lovett, in the matter of treatment, state that:[8] "A properly fitting corset with a tight pelvic hold not only improves balance, but incidentally serves as a splint and support. Proper corsets, then, accomplish three things in the relief of this condition—1. They tend to correct vicious balance by carrying the center of gravity backward, thus relieving muscular strain. 2. They partially splint the lower back. 3. They furnish an artificial annular ligament to the glutei muscles."

We may add that, as practically all the women we have seen, tortured by this sort of backache, have also suffered from movable kidney and associated visceral ptoses, the corset which we herewith present, specially designed for this purpose, will afford the much-needed support of all the thoracic and abdominal viscera, as well as immobilize the sacroiliac joints.

[8] *Loc. cit.*

DISCUSSION.

Dr. J. Madison Taylor, of Philadelphia, remarked that, however important the sacroiliac junctures were in the genesis of backache, there were, underlying this and other conditions, certain factors on which they all depended. The chief of these was posture. Faulty attitudes of body contributed to and aggravated any disturbance at the sacroiliac synchondrosis or relaxation of other skeletal structures. He sketched on the blackboard the normal, and the more frequently met abnormal, attitudes, and referred to the drag on and the physics of the movable organs as factors in back pains. Another factor was afforded in moderate or severe degrees of fibrositis and myositis, occurring not only in the grosser structures, but in the muscular parts of the organs themselves. Backache was also the outcome of loss of elasticity in the supporting structures, and the restoration of elasticity by cultivating mobility was an important means of relief. Artificial supports were of value mainly, as Longstreth had pointed out, to compel the pelvis to resume its normal position. Properly adapted belts would not only do this, but would also regulate splanchnic circulation, thus aiding in the cure of splanchnic neurasthenias. No belt or corset should do too much, or be depended on too long, or the impaired structures would lose tone, become incapable of doing their proper work, and the individual would become chronically inefficient. The corset of Dr. Gallant was an admirable one, although he would criticise the cuirass-like, massive compression it exercised on the structures above the hips. One feature he took issue with, viz.: the garter-supports in front, pulling downward. No abdominal or pelvic support should have any garter pulling down in front, which would negate the required uplift.

Dr. F. E. Stewart, of Germantown, Pa., said that he had met with a case of infectious disease of the sacroiliac joint due to typhoid fever. Some relief had been afforded by plaster casts and corsets, but a cure had not resulted. He asked the author of the paper what experience he had had in treating cases due to infection with his corset.

Dr. Gallant said that, while Dr. Taylor was not so much out of the way in the matter of treatment, in other respects his viewpoint was quite opposite to that of the speaker, and it would occupy entirely too much time to demonstrate the many points in which he differed. The whole question of attitude depended upon the way in which one looked at it. It was a serious thing to say that a corset changed the figure, but he could positively assert that his corset did change the figure. After a woman had been wearing one for some time it became necessary to refit it. The changes effected were mainly abdominal, but every structure in the trunk, including the heart, lungs, and diaphragm, was lifted and held up. The development of this corset had entailed much careful investigation and thought, and he had been working on the matter ever since 1893. Typhoid fever might cause an infection of the sacroiliac joint, setting up a diseased process, just as tuberculosis did, and in such conditions fixation of the joint with a plaster-of-Paris jacket was usually called for. Recently a case had come under his care in which sarcoma of the pelvis had produced a dislocation of the joint. Here he simply relieved the patient, from time to time, by adhesive-plaster strapping, but never expected to effect a cure. In answer to a question by Dr. Babcock as to the relation of the uterosacral to the sacroiliac ligaments, Dr. Gallant said that when the former were shortened, thickened, and stiffened, as the result of previous infection and inflammation, the dragging downward of the uterus, when laughing or sneezing, crying, or by any expulsive effort, would cause pain referred to the sacroiliac joints, not infrequently pointed out as at the sacral dimples. The diagnosis could be easily made by grasping the uterus between the fingers in the vagina and the hand on the fundus, through the abdomen, when any attempt to raise or lower the uterus would put the ligaments on the stretch and elicit the characteristic pain. The treatment of this uterosacral ligament fixation after the method of Brandt, by massage, or by forcible stretching under anesthesia, and the absorption of the thickening of the ligaments by ichthyol tamponade, was one of the most satisfactory of gynecologic procedures.

THE VALUE OF ENTEROSTOMY IN ILEUS.

By L. H. TAYLOR, M.D.,

WASHINGTON, D. C.

In the following paper I have endeavored to show the value of enterostomy under certain conditions in ileus. The conclusions are based on a series of 20 cases which have occurred in my practice during the past two years.

Despite the great improvement in the treatment of abdominal conditions in which bowel paralysis occurs, either as a result of inflammatory processes, reflex inhibition, or mechanical obstruction, there is a definite percentage of these cases which fail to improve and progress to a fatal termination. My attention was first called to the possibilities of enterostomy as a life-saver by the favorable influence exercised by the early formation of a fecal fistula in peritonitis of appendiceal origin. Up to a comparatively few years ago, before the introduction of continued proctoclysis and the postural treatment, the mortality in peritonitis following appendicitis was excessively high. The small percentage of cases that did recover developed fistulæ and bowel drainage early in the disease process.

It is undoubtedly true, to my mind, that the toxemia in these cases arises more from products contained in the lumen of the bowel than from inflammatory substances produced in the peritoneal cavity. It seems most probable that the intestinal contents in obstructive cases, whether mechanical, inflammatory, or reflex, rapidly rises in toxicity, and that the virulence of the contained organisms is also much increased. Along with this increased auto-intoxication, and of hardly less grave import to the patient, is the rapid development of tympanites. There is no one of us who has not been impressed with the mechanical interference to respiration and the ill effects of pressure on the heart due to gaseous distention of the bowel. We can minimize the toxemia by raising blood-pressure by the continued injection of salt solution, by posture, and by stimulation of excretion through the kidneys. But these therapeutic measures have little influence on the mechanical condition of tympanites and retained intestinal fluid contents. It is the cases in which distention of the bowel and stagnation of its contents are prominent that furnish us with our mortality list in peritonitis, and it is in these cases that I believe enterostomy offers a good chance of relief.

Our object in opening the bowel is to permit the escape of gas and fluid contents, and upon the ability of the gut to empty itself will depend the success or failure of the operation. The factors producing the onward flow of the fecal current are peristalsis, the contractions of the diaphragm, and those of the parietal abdominal muscles. In ileus, or at least in those cases of ileus where the condition is grave enough to warrant enterostomy, peristalsis has

either ceased or has become so feeble as to be negligible. We are then forced to rely on the contractions of the diaphragmatic and abdominal muscles to empty the overdistended and overloaded bowel. Where either of these two remaining forces is much weakened we cannot expect to get much of a result. In all the cases in which there was failure to obtain copious drainage after enterostomy, I have noticed that the abdominal muscles were either flabby, as those of fat or of old people, or had been so stretched by overdistention as to be paralyzed. In such cases the emptying of the bowel depends on diaphragmatic massage of the distended intestine, and this usually proves insufficient.

From the above it can be appreciated readily that to allow tympanites to go on to a high grade is to invite disaster, and that to expect good results in the case of old people, fat people, and those with weak abdominal muscles is to invite disappointment. The ideal time for enterostomy is not when peristalsis has ceased, but when it is apparent that it is going to cease in spite of the ordinary therapeutic measures. There are but two reliable ways to determine this, viz., by the frequent use of the stethoscope and careful observation of the character of the vomitus.

In employing the stethoscope one must not mistake for true peristalsis the gurgle of fluid in the stomach due to and synchronous with respiratory movements, or the sounds heard over the sigmoid due to fluid introduced in proctoclysis. The offending portion of the intestinal tract is the small bowel, and it is over this that we should specially listen.

Of hardly less importance as an index to approaching bowel paralysis is the character of the vomitus. The pyloric sphincter gives way as a part of the general process of bowel distention, and permits regurgitation into the stomach of the intestinal contents. When the vomitus loses the ordinary sour gastric odor and takes on that of the small bowel, and when first it is bile-stained and then becomes brown and contains black specks of altered blood, we have proof almost positive that the motor function of the bowel is abolished.

When it has been decided that an enterostomy is indicated, it becomes necessary to determine whether or not anesthesia should be employed. As in most of these cases the abdomen has recently been opened for some primary condition, it will be necessary only to cut and remove one or more of the sutures closing the original wound to reopen it. If the patients are nearly moribund, sensation is so much obtunded that no anesthetic is needed. When this is not the case, I have had the patients given a light primary ether anesthesia. In reflex ileus where there has been no previous incision I have used a local anesthetic consisting of 1 per cent. alypin and ¼ per cent. quinine and urea hydrochloride solution. A patient requiring enterostomy for ileus is in no condition to be moved. The operation should be performed in the patient's room, and, furthermore, the operative procedure should be of the simplest and quickest. It is my firm conviction that a slow, deliberate operation with the usual operating-room paraphernalia, technique, and courtesies will kill every patient.

The technique I have employed has been as follows: After the peritoneal cavity has been opened the index finger and thumb of the left hand are

inserted and a loop of distended ileum as near to the ileocecal junction as possible is picked up: a ringed sponge forceps is passed in and the loop grasped and drawn up to the abdominal opening. No time should be lost in trying to make sure that the loop is the lower ileum;—the best we can do is to be sure it is distended ileum and comes from the right lower quadrant. Two Pagenstecher linen sutures are passed through all the coats of the intestine transversely to its long axis and opposite the mesenteric attachment. They should be about half an inch apart. Between them a pair of sharp-pointed scissors is plunged into the lumen of the gut and the blades separated, thus making an opening with the minimum of cutting of the muscle fibers. A rubber tube of not less than $\frac{5}{16}$ inch inside diameter, with the end fenestrated and bevelled, is inserted for two inches and sewn in by the two linen sutures previously passed. The loop of gut is dropped back into the cavity and then drawn up to the parietal peritoneum by the tube. While it is in this position a silkworm gut through-and-through suture is passed through the wound margins, skin, fat, fascia, and tube, to hold it in this situation. It is not necessary to stitch the gut to the peritoneum; this wastes time and does no good. The danger of escaping intestinal fluids infecting the peritoneum is more imaginary than real. The little infection that does take place is local and the resulting adhesions walling off the general cavity are conservative.

It is extremely important to get the enterostomy opening low down in the ileum, for two reasons: 1. The farther away it is from the pylorus, the larger the area of distended gut that will be drained. 2. The farther away from the pylorus, the less acid will be the character of the discharge which later will be thrown out over the skin, and the less the interference with nutrition when food can be resumed and the wound left to heal. The fistula should never be made into the large bowel, as this would materially interfere with the proctoclysis, which should always be employed.

In appropriate cases, in which the abdominal muscles are not stretched beyond their limit of tonicity and in which the intestines still possess some power, the relief is immediate. The quantities of gas and fluids that are discharged are enormous. Usually these patients are so nearly dead that changing the bedding and dressings should not be permitted for several hours. As a rule, patients when much distended cannot retain salt solution even when it is given very slowly by rectum. It will be noted, however, that they improve in this respect soon after drainage of the bowel is established. One of the most striking results is the cessation of vomiting: this takes place almost at once and the symptom does not recur as a rule. If it does, gastric lavage, to clean out bowel content which regurgitated before the enterostomy was done, will usually suffice to check it. The character of the pulse both as to volume and rate soon improves. There is in a few hours a change in the patient from the appearance of imminent death to one of comparative safety.

The stay silk-worm-gut suture is left *in situ* for four or five days. When it is removed, a large safety pin is passed through the tube in such a way that it rests on either margin of the wound. In two or three days more the Pagenstecher sutures cut out of the bowel and the tube comes away. The resulting

fistula heals rapidly if the edges of the wound are pulled together and kept so by adhesive plaster. It is important to protect the skin with some thick ointment and to see that the fistulous discharges do not work their way under the plaster, as they are intensely irritating. I have found it necessary to resort to operative intervention to close fistulæ in but two instances.

It is of course impossible to say a given patient would not have recovered if a certain therapeutic measure had not been used. But so far as my individual judgment goes, I have no hesitancy in saying that I believe every one of the 20 of my series would have died promptly unless enterostomy had been performed. At least half appeared almost moribund, and in all every effort had been employed without avail to obtain bowel movement by the use of cathartics, purgative enemata, and eserine used hypodermically.

Of the series, 16 were cases of peritonitis due to various causes, 2 were incident to toxemia from disease outside of the abdominal cavity, 1 followed on the third day after a high forceps delivery with subsequent post-partum hemorrhage, and 1 was reflex.

Among the peritonitis cases appendicitis caused 10, intestinal obstruction 2, cesarian section after infection of the uterus by forceps 2, and pyosalpingitis 2. Of the 2 toxemic cases, 1 was due to lobar pneumonia in a woman eight and a half months pregnant, and the other to a general gas-bacillus infection in a woman operated on for a large, partially strangulated, pedunculated fibroid of the uterus. The case of reflex ileus developed on the twelfth day after a clean posterior gastroenterostomy for ulcer at, and partially obstructing, the pylorus. In this case there was also enormous dilatation of the stomach.

In the series there were 15 recoveries and 5 deaths; 2 of these latter can be fairly excluded from the mortality percentage: 1 was the case of gas infection with the *Bacillus aërogenes capsulatus*, which was of course hopeless from the start. The other was the case of pneumonia which died of acute cardiac dilatation after the condition of ileus had been relieved by enterostomy and the patient had been passing gas and feces by the anus. Of the remaining 3, 1 was a case of resection of a gangrenous sigmoid from volvulus in a woman. Here after ileus developed the enterostomy was done in the colon, and as a result the salt solution given per rectum promptly escaped and was not absorbed. I am convinced that her death was largely due to this fact. In the remaining 2, while some relief was secured by enterostomy, the patients eventually died from toxemia. If we exclude the cases of gas infection and pneumonia, the series shows a mortality of 16.6 per cent. If enterostomy had not been done, I am sure it would have been 100 per cent.

I report 1 case of the series as typical of what can be accomplished by enterostomy in the terminal stages of ileus:—

Mrs. E. P., widow, 21 years of age. History negative save for three previous attacks of stomach trouble. Admitted to Sibley Hospital August 26, 1911, suffering from an attack of acute appendicitis. Was put on routine treatment, and in a few days the symptoms cleared up. The patient was operated on September 2, 1911, a clean appendectomy being done. She made a rather uneventful recovery, the stitches being removed on the eighth day, when the wound was found in good condition. Her temperature

was 98.6° and her pulse 80. The next day she began vomiting for the first time since the day of operation. The vomitus consisted at first of undigested food and later of a amount of fluid was so large that I collected it and had it measured. The hospital sidered to be an attack of acute gastritis and treated as such without any relief. At this time, September 13th, at 6 A.M., her temperature was 97.6°, pulse 112, and respiration 26. There was continued vomiting of bile and beginning distention. She was put on eserine salicylate, gr. $\frac{1}{30}$, and sparteine sulphate, gr. iss, hypodermically every four hours; salt solution continuously, and given calomel, gr. ss, by mouth every one-half hour for 6 doses. Turpentine stupes were applied over the abdomen and during the day purgative enemata used four times without result. At 10 A.M. her temperature had dropped to 95°, her pulse had risen to 120, her abdomen was much distended and rigid, and there was scarcely any audible peristalsis. At noon hypodermoclysis was instituted. Temperature 97.6°; pulse 140, very feeble and irregular; distention worse, vomitus becoming brownish in color; patient cyanosed. At 2 P.M. gastric lavage was done and 6 ounces of castor oil left in the stomach. Her condition continued to grow worse steadily. At 7 P.M. audible peristalsis had entirely ceased, the distention was enormous, and there was almost continuous vomiting of dark-brown intestinal content. Her pulse was 168 and nearly imperceptible at the wrist. Without anesthesia the original incision, made eleven days previously, was opened and a loop of ileum drawn up and incised. During the operation the patient became pulseless, respiration ceased, and her pupils dilated widely. It was necessary to resort to artificial respiration for some time before she revived. Within ten minutes after the opening of the bowel nearly three quarts of a light-yellow, very offensive fluid escaped, in addition to large quantities of gas. The amount of fluid was so large that I collected it and had it measured. The hospital records show that the dressings were saturated with discharge on an average once an hour for the next twenty-four hours. Her convalescence was a stormy one for the first six days, but improvement was steady. Her nausea ceased for twenty-four hours and then recurred, when it was controlled by gastric lavage. She was given salt solution continuously by rectum for six days and was put on brandy and whey by mouth immediately. The stimulation consisted of alternate hypodermics of digitalin, gr. $\frac{1}{10}$, and sparteine sulphate, gr. iss, so that she got one or the other every three hours. On the fourth day after operation the tube was removed. The fifth day she expelled gas from the rectum, and on the eighth day had her first stool. Fecal matter ceased to exude from the fistula on the thirteenth day; bile escaped until the eighteenth day. The opening closed without operation. Her progress after the sixth day, with the exception of an attack of acute gastritis from imprudent eating on the nineteenth day, was uneventful. During this attack her pulse in twelve hours ran up from 90 to 140 and became very irregular. The patient left the hospital October 17th, thirty-seven days after the enterostomy, in good condition.

I have examined her within the last ten days, eight months after the operation, and find no hernia. She complains of no pain and has no tendency to constipation.

The conclusions I feel justified in presenting are:—

1. Enterostomy offers an excellent chance to a class of ileus cases formerly always fatal.

2. It should be performed before intestinal paralysis is complete and before the abdominal muscles are stretched beyond their limit of tonicity.

3. The lower ileum should be the region of election for the operation, and a tube of not less than $\frac{5}{16}$-in. inside diameter used for drainage.

4. The opening should not be made in the colon.

5. Old people, fat people, and people whose abdominal muscles are weakened from any cause offer an unfavorable prognosis.

DISCUSSION.

Dr. W. Wayne Babcock, of Philadelphia, said that in cases such as those mentioned in the paper the danger of the operation was very great. In a small number of patients in which he had tried to relieve the condition by an appendicostomy or by an incision or the introduction of a tube into the bowel, death had been almost invariable. Fortunately, under modern methods, postoperative ileus was rarely seen, as compared with previous years. A simple and remarkably efficient method of treating certain forms of ileus had been suggested to him by two experiences: The first was that of an elderly man who had been treated unavailingly for a number of days for intestinal obstruction. After administration of spinal anesthesia, and as the incision was about to be made, there was a gush of fluid under the operating table which was discovered to be due to a large liquid evacuation. In a second case, an old man had likewise been treated for four or five days, but no gas or solid material passed the bowel; the abdomen progressively became distended, and fecal vomiting was present. Just after the administration of spinal anesthesia, and as the operator reached for his scalpel, there was a gush of fecal material mixed with gas from the rectum, and on pressure upon the abdomen the meteorism disappeared as from a collapsed paper bag. In a recent case, that of a girl who had had no less than 27 abdominal operations, a number of which were for ileus, and with dense intra-abdominal adhesions, a postoperative ileus, which resisted treatment, developed two or three weeks after the operation. Guided by the previous experiences, after an ineffectual trial of the conventional measures, the patient was given spinal anesthesia, and in a few minutes later there was a free passage of gas, fluid, and semisolid fecal material. Spinal anesthesia he believed to be the most potent medicinal agent at present known for the relief of ileus. It cut off inhibition to the bowel, releasing the intestinal ganglia, and at the same time gave a very complete relaxation of the sphincters. There followed, therefore, a marked contraction of the caliber of the bowel and very active peristaltic movements. Repeatedly, in operating in other cases of intestinal obstruction, the speaker had noted an evacuation before the completion of the operation. In certain mechanical forms of ileus he believed that spinal anesthesia would be potent in relieving the obstruction, while all forms of spastic or adynamic ileus would probably be relieved by this simple measure. He advised, therefore, that in postoperative as well as in many other forms of ileus the patient before operation be given the test of spinal anesthesia. If it failed, operative intervention could immediately be instituted. While this procedure was of considerable value for purposes of diagnosis, it should be remembered that it also was effective in forms of inflammatory ileus, such as those due to purulent peritonitis requiring drainage. To be efficient, spinal anesthesia should produce complete anesthesia and relaxation of the abdominal walls. He believed the intradural injection would in the future enable surgeons to avoid many operations for ileus at present considered necessary.

Dr. Taylor said that his cases were not operating-room cases. If they had been taken to the operating room they would certainly soon have been in need of an undertaker, and not a surgeon. They had therefore been kept in their own beds, and operated as promptly as possible. If they were in bad condition, no anesthetic was given at all. The hospital cases of which Dr. Babcock had spoken were anomalies, and not the kind of cases referred to in his paper. The treatment he had described he would advise only in *suitable* cases, and in these relief could certainly be afforded in a fair proportion of instances. He believed that if these patients were operated in their beds much time could be saved and much shock and exhaustion avoided.

THE MEDICAL TREATMENT OF GASTRIC AND DUODENAL ULCER.

By LOUIS M. GOMPERTZ, M.D.,

Clinical Instructor of Gastrointestinal Diseases, Yale University,
NEW HAVEN, CONN.

The modern practice of medicine depends so largely upon proper diagnosis that the study of symptoms almost overshadows the application of treatment. With respect to medication proper, advances are being made, but in the field of diagnosis the immediate future is rich in the promise of achievement which will give a greater insight into the exact nature of disease. Already the trained and skillful diagnostician has developed a well-defined specialty of his own, and he is consulted frequently in cases where conflicting symptoms leave the average practitioner puzzled how to proceed.

It is an elementary proposition that a careful and detailed diagnosis is necessary before one attempts to prescribe for the ordinary ailment or disturbance. Consider, then, how important and essential it becomes to develop, by careful study and observation, a thorough, comprehensive diagnosis of complaints such as gastric and duodenal ulcer, the presentation of which I propose to bring to your attention in this short paper. An early diagnosis, such as has been suggested, at the very outset of the case is particularly desirable, because the conditions present, if not in aggravated form, may still respond to medicinal and dietetic treatment, which will probably give permanent relief; whereas the failure to diagnose until delay has permitted a chronic condition to develop may subject the patient to what he considers the dreaded surgical operation, with its possibly fatal consequences.

Only within recent years has it become possible to recognize, with any degree of certainty, the existence of gastric and duodenal ulcer. No longer are these conditions displayed as post-mortem curiosities; but now, with the aid of exact and searching diagnoses, we are able to effect cures in many instances, by medicinal or surgical means. I venture to say, from experience and observation, that in many cases of so-called neurasthenia the real seat of the trouble has been the particular form of ulcer under consideration, and that the failure to identify this condition through inaccurate or delayed diagnosis has driven patients to find expected relief in nostrums and patent preparations.

The treatment of gastric and duodenal ulcer is practically the same, and will be so considered; but in neither case can there be any specific treatment. The diagnosis having determined with reasonable certainty the location of the ulcer and its probable duration, the plan of treatment to be followed presents the final question; and incidentally, the problem how to maintain nutrition during that time has to be considered.

Our immediate concern, however, is with the character of the ulcer, for, according to the classification that I have adopted, we shall find it to be either acute, subacute, or of the chronic, indurated form. A word with respect to each for purposes of identification: The *acute* form is the ulcer accompanied by sudden hemorrhage, particularly where no history of previous digestive disturbances has been obtained. This would be the easiest form to diagnose were it not for the fact that incidentally it must be determined whether or not perforation has taken place. The *subacute* ulcer is generally indicated by its history to be of very short duration: still, this, as well as the last form, may present acute exacerbations and, with some of the classical symptoms of ulcer lacking, the diagnosis is apt to be overlooked. This ulcer of short duration generally responds to dietetic or medicinal treatment, and, although there be recurring symptoms, there is wanting the appearance of a progressive disease. The *chronic, indurated* ulcer is that form which has extended over a long period of time, and may be differentiated from the other forms by its persistent and progressive character, as well as by its resistance to all medicinal measures and failure to respond thereto. It must be apparent that the attempt to define sharply these forms of ulcer is extremely difficult and taxes to the utmost the resources of the clinician, but the endeavor should be persisted in with a view to determining the stage of the ulcer or its period of duration, so that the question of medical or surgical treatment can be definitely decided.

We are now concerned with the location of the ulcer, and we proceed to determine the position by its point of attack. In this way we may find the ulcer at the posterior wall, the lesser curvature, the pylorus, or the duodenum. Statistics are so varied that it is rather difficult to state definitely which parts are more frequently affected. If the location is at the pylorus and the duration has been sufficient to cause a beginning cicatrix with symptoms of stenosis, the only resort is to surgical operation; the same is true of the chronic, indurated form in other portions of the stomach, and medicinal treatment is of no avail. The finding of food remnants, sarcinæ, etc., with the stomach in a fasting condition, is usually evidence of stenosis of the pylorus due to the cicatrix of an ulcer. My experience has been that it is a waste of time and medicine to treat this condition medically.

With respect to operative methods to be followed there is a diversity of opinions among surgeons almost as great as there is among physicians respecting medical treatment. Whatever the method employed may be, we are interested in the fact that numerous cases in which operation was advised fully confirmed the previous diagnosis, both as to location of the ulcer and the length of its duration, thereby showing the absolute necessity of affording to the patients surgical relief.

We are more concerned at present, however, with the medical and dietetic treatment of ulcerative conditions, and also with the problem of maintaining adequate nutrition during certain phases of the treatment. On the one hand, we have numerous reports of cures from the so-called "feeding" method, the idea first proposed by Lenhartz having been followed, even in

cases where hemorrhage is a concomitant symptom; on the other hand, we have just as many reports of cures from the so-called "starvation" treatment. Then there is the serum treatment, the method of injecting bacterial vaccines, and numerous other "ulcer cures," each with its own strong adherents. No doubt, each of the methods named has some particular virtue, but, instead of adopting any one of them, I have been led by experience in the treatment of ulcer to develop a distinctive routine procedure, with modifications to suit the individual case.

Fig. 1.—Rectal feeding apparatus.

When I am fully satisfied that the conditions present point to the existence of ulcer, I order the patient to bed, and insist that he have absolute rest in the fullest sense of the word, mental and physical. No food at all is allowed by mouth for a period of from five to seven days, or sometimes longer, according to the progress of the case, which must be closely observed. Even if acute hemorrhage has taken place I am inclined to doubt the necessity of operating during that period, unless actual perforation is suspected and confirmed. Until the hemorrhage has positively ceased, I advise giving morphine hypodermically; an ice-pack should be placed on the abdomen, and if necessary the bowels should be moved by an enema. Under no circumstances should food by the mouth be permitted. In the absence of hemorrhage,

hot applications in some form, preferably the electric pad, may be placed over the abdomen. This, I believe, tends to improve the intra-abdominal circulation, and thereby assists in the healing process. The bowels should then be moved by citrate of magnesia or Carlsbad salts, which also aid in the reduction of the acidity. After the bowels have been freely moved, 30-grain (2 Gm.) doses of bismuth subnitrate should be given, in combination with 7½-grain (0.5 Gm.) doses of magnesium hydrogen dioxide (25 per cent.),

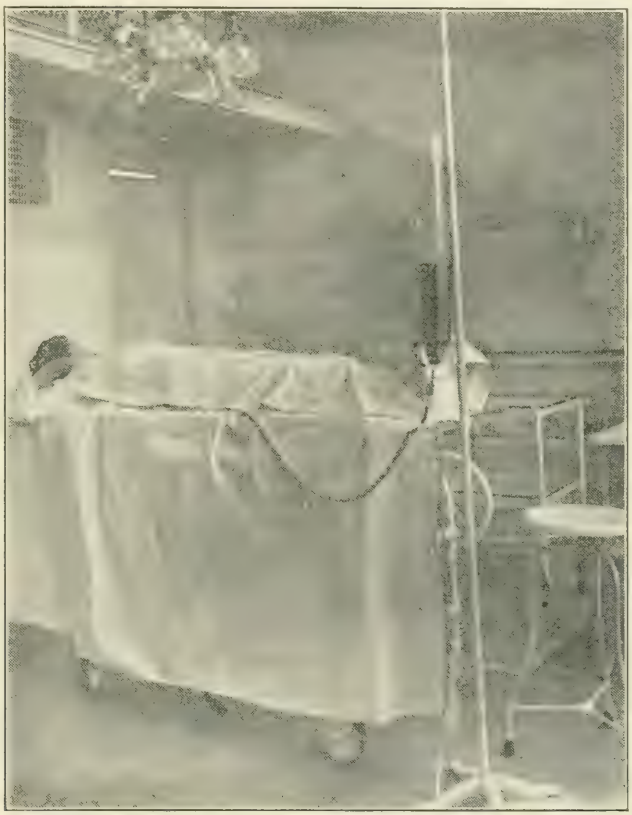


Fig. 2.—Apparatus in use.

to be taken three times daily. In order to insure the retention of these drugs, it may be necessary to use small quantities of boiled water.

In the cases under consideration we are next confronted with the question, how to maintain nutrition during the treatment. I recommend immediate rectal feeding,—not that I believe rectal alimentation is adequate to supply sufficient nourishment for any considerable length of time, but because I have found by experience that it is useful in preventing the untoward effects of complete starvation. The composition of the nutrient enema to be used has aroused considerable discussion, and there already exists an extensive literature upon the subject. Such authorities as Edsall and Miller claim, as a

result of their experiments, that fats and proteins are poorly absorbed by the rectal mucous membrane. My own experiments in rectal feeding incline me to the use of dextrose solution, and I have found that a considerable amount of this substance can be absorbed. The administration of solutions of dextrose, in the great majority of cases, has supplied sufficient nutrition to tide the patient over the required period of rectal alimentation. To 500 c.c. (1 pint) of normal saline solution there has been added 50 Gm. (1½ ounces) of dextrose, making a 10 per cent. solution of the latter. Every six hours this solution is introduced into the rectum at body temperature, according to the method which I shall presently describe. If the entire solution were absorbed, it would mean that 200 Gm. of dextrose, representing approximately 800 calories, would be supplied to the patient every twenty-four hours. My experiments have shown as high an absorption as 193 Gm. of dextrose, the equivalent of over 700 calories, or a little more than one-third the number of calories required to sustain the body at rest. I consider these results so gratifying that I do not hesitate to recommend the use of dextrose as indicated. Furthermore, it has been tried successfully in cases of ulcer at the Hospital of St. Raphael, New Haven, Conn., and likewise in many other instances where rectal feeding was necessary because no food could be taken by the mouth.

For the administration of these nutrient or saline enemas, I have designed a rectal feeding apparatus[1] which permits the solutions to be taken into the rectum at body temperature, according to the Murphy drip method.

This apparatus consists of an inverted caloris vacuum bottle, with metallic exterior case, suspended by a handle. The mouth of the bottle is fitted with a two-hole rubber stopper. One hole has a glass tube for the ingress of air inserted into it; the other has a glass T-tube as outlet. At the lower end of this T-tube is attached a soft-rubber tube for dispensing the contents. The side outlet is connected with a hook-shaped glass tube serving as a gauge glass and showing at all times the quantity of fluid in the bottle. The soft-rubber dispensing tube is attached to the glass drop chamber, wherein it is possible to see the quantity and rapidity in which the solution is dispensed; this is controlled by a special pressure device, which acts on the outer surface of the soft-rubber dispensing tube. Directly below the lower end of the glass drop chamber, a special glass connecting tube, with elbow, is inserted, the vertical section of which is somewhat smaller in lumen than the elbow. The object of this attachment is to admit of free passage of the solution to be used, whereas the elbow, through its upward turn and larger lumen, will admit of a still more free escape of such solutions and gases as may from time to time be expelled by the intestines. To control as accurately as possible the quantity of the solution injected, the white soft-rubber tube attached to the elbow referred to above is led half-way up to the top of the equipment, in order to offset the force with which the solution is ejected from the body. This tubing then leads into a basin. The soft-rubber dispensing tubing is of a maroon color, about four feet long, and is covered by a removable

[1] Manufactured by Knauth Brothers, New York City.

woven asbestos insulation, which prevents loss of heat from the solution passing through. At the distal extremity, this dispensing tube is intercepted by the insertion of a thermometer and ends with a glass conic nozzle onto which the catheter or other tube leading directly into the body is attached. The solutions are placed in the container, at boiling temperature, and delivered at body temperature. One feeding usually takes about three hours.

During the period of treatment, indications such as care of the bowels, relief of pain, of hyperacidity, etc., should be met as they arise. The return to feeding by the mouth should begin as soon as possible, according to the patient's condition. Great care should be taken, however, in the foods selected. I usually begin with small doses of albumin water, given several times daily. If this is well tolerated, oatmeal gruel which has been thoroughly cooked in a steamer and strained through cheesecloth is then given in small doses. For the sake of variety, a thick barley soup, strained, may be given. Some patients are able to take milk that has been diluted one-half with lime water, or peptonized, while others are unable to take it in any form. However, I am not overenthusiastic about the giving of milk in these cases. Thickened soups and scraped meats, broiled, may then be given. If the case progresses favorably, the diet may be gradually increased.

After feeding by the mouth has been started, rectal alimentation may be decreased or entirely stopped. It is extremely important to caution patients concerning their diet after they cease to be under observation, and I am in the habit of giving specific directions, in writing, regarding it.

Thus I have endeavored to present to you briefly my routine treatment of gastric and duodenal ulcer. I have investigated and experimented with various forms of treatment described in the textbooks, or which have appeared in current medical literature, but the results have not been encouraging. It may be urged that the rectal method is old-fashioned, but that objection does not detract from the value of the treatment, which has proven successful in a number of cases that have come under my personal observation. It possesses every advantage that can be claimed for any rational treatment. It is simple, can be given at the home of the patient, and causes him little or no discomfort. At all events, while waiting until a better or a specific cure for ulcer shall have been introduced and accepted by the profession, I have ventured to submit to you these few suggestions for what they may be worth, and in the hope that they may serve a useful purpose in affording relief to patients suffering from gastric or duodenal ulcer.

A NOTE ON THE TREATMENT OF THE GASTRIC NEUROSES.

By REYNOLD WEBB WILCOX, M.D., LL.D.,

Formerly Professor of Medicine at the New York Post-Graduate Medical School and Hospital; Consulting Physician to St. Mark's and to the Nassau Hospitals,

NEW YORK, N. Y.

THE neuroses of the stomach are generally enumerated as twelve: Two secretory,—hyperchlorhydria and hypochlorhydria (including achylia gastrica); six motor,—cardiospasm, pylorospasm, gastric hyperperistalsis, merycism, nervous eructation, and cyclic vomiting, and four sensory,—gastric hyperesthesia, gastralgia, bulimia, and anorexia nervosa. Formerly all of these conditions were grouped together under the title "nervous dyspepsia," and perhaps from the therapeutic standpoint this was not so illogical as might be supposed. The refinements of the chemical analysis of gastric contents, however, the methods of physical exploration of the stomach, and the facility with which its motor functions are now determined by modern procedures have contributed to a differentiation of disordered function in which perhaps too much stress is laid upon a symptom-diagnosis, or, at least, too much importance is attributed to one predominant manifestation, for the permanent well-being of the patient.

Accuracy and even refinement in diagnosis are by no means to be deprecated; on the contrary, they are to be encouraged, but in the careful cultivation of the narrower field the greater general condition is not to be lost sight of, nor its existence ignored. From the standpoint of the therapeutist, even the substitution of the term "gastric neurosis" for nervous dyspepsia has not been altogether fortunate, for it has favored the conception of a gastric neurosis as a morbid entity. Were this not the fact we should doubtless never hear the surgeon advocating the operation of gastroenterostomy for nervous dyspepsia, while it is not infrequently recommended for a gastric neurosis. Even more remarkable is the earnest argument of a surgeon, better known for his mechanical ability than for his professional knowledge, in advocacy of his particular method of "sewing up a gastric neurosis." Language is given to some for the confusion of their ideas. By patients the symptoms are sometimes described as the result of a "gas house alternating with a vinegar factory," and a careful interrogation as to signs and symptoms may verify the homely metaphor. The tenable conclusion is that the chemistry of gastric secretion and the physics of stomach motility are not elucidated in textbooks built on an isolated laboratory investigation. They should be predicated upon what the organism may do when its pathology is physiology gone wrong, and a neurotic subject is doing his, or generally her, utmost in the way of vagaries. However, when repeated investigations are conducted the basic condition is apparent and the details, considered in their proper perspective, only empha-

size it. Again, the paresthesias may be clinically misleading: the heartburn, waterbrash, or matutinal vomiting is generally characterized as *sour*. The reaction to litmus may be neutral or even alkaline, and is but rarely acid. The lesson to be learned is that repeated examinations should be made to the end that the dominant or usual condition may be determined, and a correct diagnosis established; the latter is important chiefly in so far as it may define our therapeutic efforts. Thus, what has been assumed to be an achylia gastrica may prove to be merely gastric hyperperistalsis.

In general, to the treatment given under the several divisions of the subject, as presented in the standard textbooks on medicine or in the special works on gastric disorders, but little exception can be taken. When sufficient observation has been directed to the patient, so that the diagnosis is reasonably correct, the indications are generally well met by what is found in the books. Criticism is, however, needed to limit the apparently extensive and improper use of sodium bicarbonate in the treatment of hyperchlorhydria. Reflection and a more careful study of the chemistry of gastric secretion should lead to the substitution of *magnesium oxide* if one looks for permanent benefit.

It is important to call attention to the diet, which should be selected not so much in accordance with the chemical reactions of the stomach contents as with the condition of the patient, *plus* that of the gastric processes. It should be remembered, too, that quantitative as well as qualitative regulation is important; by proceeding thus, distinct prohibition may be eliminated. Further than this, exercise, and above all occupation, electricity, baths, and massage, so far as they may influence general conditions, should be more carefully considered and more intelligently and frequently employed. Of remedies directed toward the nervous system, many are useful, but discretion must be exercised, in order that they may have no deleterious local effect. The use of sedatives and especially of narcotics is particularly to be deprecated. Even more forcibly is the habitual employment of "pick-me-ups," bitters, and cocktails, especially the abominations in vogue in fashionable restaurants, to be interdicted.

As there is no panacea for the neurotic condition which dominates the individual, and of which the gastric neurosis is only one expression, so there is no specific for any one of the twelve varieties of gastric neurosis. Each individual must be studied as an entire organism. With many neurotic women in the higher walks of life, in addition to the regulation of habits and the employment of physical agencies, as already mentioned, much benefit often comes from the administration of 10 drops of the tincture of nux vomica, 6 grains of resorcinol, and 1 dram of peppermint water diluted in 2 ounces of water after meals. This will often obviate the necessity for other medication.

This brief paper should not be construed as showing any lack of appreciation of what gastrologists have given to scientific medicine; nor does it ignore much of modern surgical work, which has been epoch-marking. It is a plea not for the less consideration of morbid gastric processes, but for the paying of more and better attention to an individual who is so unfortunate as to possess an unruly stomach.

FILARIASIS; REPORT OF CASE TREATED WITH DIOXYDIAMIDOARSENOBENZOL.

By NOBLE P. BARNES, M.D.,

WASHINGTON, D. C.

While known from antiquity, confused at times with leprosy, and a general term used by the ancients—Arabian and Greek physicians—to designate various "distempers," elephantiasis in its true sense is of modern understanding. Since this name expresses but one form of a general infection, the newer term filariasis is more acceptable.

In 1863 Demarquay discovered a larval nematode (*Microfilaria Bancrofti*) in the fluid of chylous dropsy of the tunica vaginalis. From 1866 to 1868 Wucherer found the same organism in the urine of a number of cases of chyluria. In 1870 Lewis made similar observations in India, and in 1872 discovered the blood of man to be the normal habitat of this larval parasite, which he named "*Filaria sanguinis hominis.*" In 1876 Bancroft discovered the adult form and Cobbold named it "*Filaria Bancrofti.*" Since that time Manson and other workers have demonstrated the mosquito to be the intermediary host. *Culex fatigans* was the first carrier discovered, but several species of mosquito may subserve.

The human circulation is the habitat of the larvæ of possibly six distinct species of filariæ. The two of pathological importance are the *Microfilaria Bancrofti*, or *nocturna*, the adult inhabiting the lymphatics of man, and *Filaria diurna*, or *loa*, which lives in the subcutaneous tissue. There is abundant proof that these are the etiological factors in endemic chyluria, lymphatic varix, lymphatic scrotum, elephantiasis, and other obscure tropical diseases.

The prevalence of *Filaria Bancrofti* is extensive in parts of the tropical and subtropical countries. One-third of the inhabitants of Samoa, the South Sea Islands, and the Friendly Islands harbor blood filariæ. In some parts of south China and the western coast of Africa one-half of the population is thus infected. In the latter location, according to the claim of recent investigators, the men who do not have elephantiasic enlargement of the scrotum are regarded as abnormal. The prize scrotum thus far reported weighed 224 pounds and was carried about in a wheelbarrow by its proud possessor,—as one writer expresses it: "a grotesque example of satisfaction with misfortune."

The filarial periodicity is an interesting feature and occasions the addition of another word, making the full appellation "*Filaria sanguinis hominis nocturnis.*" Manson has demonstrated the microfilaria in the larger arteries and lungs during the day and suggests that the object of the nightly swarming is a necessary corollary to the life habits of its liberating agent, the mosquito.

That the parasites are capable of decided longevity is recognized by all observers.

True elephantiasis is never entirely recovered from; it is intermittently but progressively increasing. Treatment, medicinal, mechanical, or surgical, has been unsatisfactory or useless, and the only possible means of escape is by protection from the mosquito. I refer to this longevity in anticipation of a question that may be suggested in the following report:—

Lillian Johnson, colored, 38 years old; cook; living at No. 8 Gordon Avenue, Washington, D. C., was admitted to the Casualty Hospital October 9, 1911.

Family History.—No knowledge of grandparents. Mother died of pneumonia at 45; had been previously in good health and very fleshy. Father is a large man, was always well, and is living at the age of 89. Three sisters and four brothers, all alive and well. Tuberculosis, venereal diseases, etc., negative.

Previous History.—The patient was born at Annapolis, Maryland; she had mumps and pertussis during early childhood and entered womanhood at the age of 14. She married at 24. Her husband died six years later of apoplexy. She gave birth to two children. The first, in 1899, weighed 11 pounds, grew very rapidly, and died in its fifth month. The second, born in 1902, weighed 8 pounds, and died at the age of 4 years. This child was also very large. Both children died suddenly.

Eight years ago she ran a nail in her right leg. A month later the bone was curetted and a skin graft made. Recovery was complete and she left the hospital in five weeks. For three years she had experienced a shortness of breath on exertion. Her habits generally are good. She ingests a large amount of vegetable foods; tea and coffee in moderation; beer occasionally. She uses an excess of salt; drinks large quantities of water, and urinates eight or ten times a day. For the last ten years she has been weighing in the neighborhood of 380 pounds.

About four months ago her legs became scaly. On September 16, 1911, while running for a street car, she fell and injured her abdomen and legs. From that time she claims her feet and abdomen began to swell, the enlargement progressing steadily to the present state. The bowels have always been regular.

Patient has spent most of her life in this neighborhood. As an expert cook she is sometimes taken to the summer homes of wealthy families. Four years ago she spent the summer in Nova Scotia, the winter in Baltimore. Three years ago she was at Black Island for the summer and in Washington during the winter; two years ago at Saratoga for the summer and in Baltimore for the winter; last summer at Newport, Black Island, and New York City. About five months ago she served a stag supper at Culpepper, Virginia, this being the farthest south she has ever been. She remained in Culpepper only two days.

Physical Examination.—Expression and general appearance good. Dorsal decubitus: Bones are large, muscles flabby, and nutrition good. Entire body is excessively fat. Skin is warm and moist, except on lower legs, where it is dry and scaly. Hair is thick and in good condition. Finger-nails normal. Toe-nails thick and brittle. Right leg shows scars of a previous operation. Entire right thigh and leg and left leg greatly enlarged. Right patella not palpable. Abdomen large. Heart and lungs normal.

Measurements in Inches:—

	Right.	Left.
Thigh	32	31
Midthigh	36	29
Knee	32	18
Calf	31	27
Ankle	20	21
Instep	12	15½

Fig. 1.—Patient before arsenobenzol treatment.

Fig. 2.—Patient before arsenobenzol treatment.

On October 19, beginning at 8 P.M., hourly examinations of the blood were made and by midnight microfilaria recognized. Two hours later they were sufficiently numerous to make us lose sight of everything else in the field.

Blood Examination:—

Hemoglobin	30 per cent. Dare
Red cells	3,500,000
Leucocytes	11,500
Malaria	Negative

Fig. 3.—Patient after arsenobenzol injections.

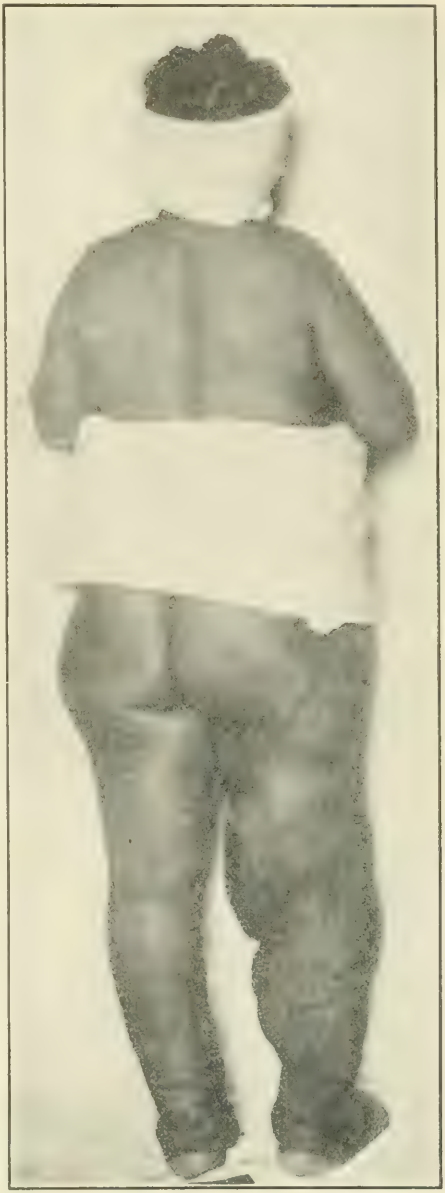


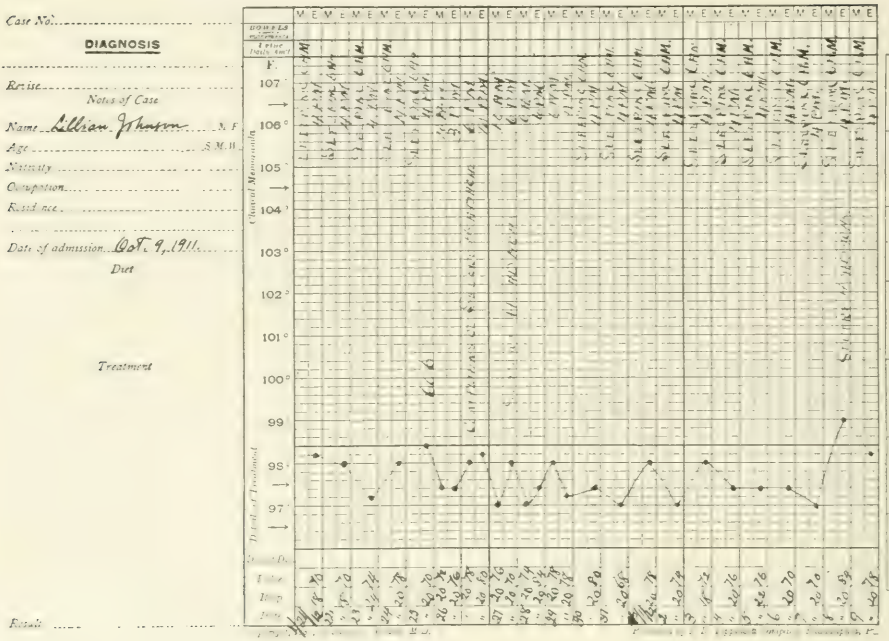
Fig. 4.—Patient after arsenobenzol injections.

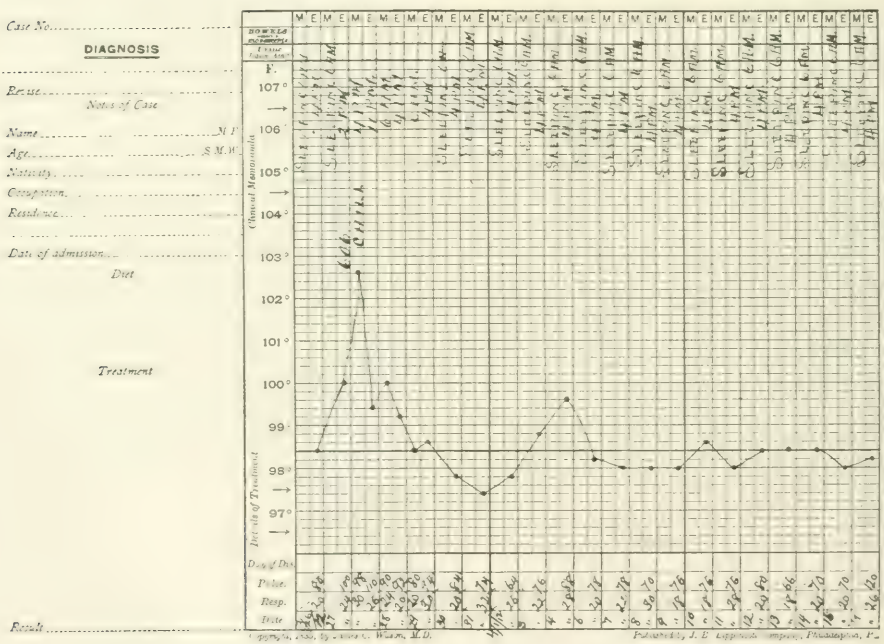
Later the microfilariæ were found in the patient's stools.

A few days after, the patient was found to be pregnant. On December 9, after an indifferent labor of forty-eight hours, forceps were applied and a 7½-pound male child delivered. The mother's urine at this time contained albumin, blood, and squamous epithelium.

Recovery from labor was slow and uneventful. Microfilariæ were found in the meconium and the blood from the cord. The mother's milk was examined from time to time and the organism found.

RECORDS OF TEMPERATURE AFTER ARSENOBENZOL INJECTIONS.





The child's blood was examined two weeks after birth and again four weeks later; each time the specimens showed the presence of microfilariæ. There was a considerable enlargement of the cervical, facial, axillary, and inguinal glands. This glandular thickening and a puffiness about the child's face and neck were the only symptoms manifest.

December 25, at 11 P.M., 6 dg. of dioxydiamidoarsenobenzol were given intravenously. An hour later the patient had a severe chill and fever. Headache was constant for the next twenty-four hours. This was followed by considerable drowsiness. By the 29th the patient was comfortable and apparently improved. The areas of induration on the legs were softer and painless. Distress and tenderness in the groin had disappeared. Patient felt much stronger and thought she was much lighter in weight.

January 10, 1912, the patient was up and walking about the room. Repeated examinations of the blood demonstrated microfilariæ still present, but in less number.

March 27, at 9 A.M., another 6 dg. of dioxydiamidoarsenobenzol was administered intravenously. At 2 P.M. there were severe headaches and chills, the temperature reaching 102.6° F.; pulse, 110. She had a comfortable night, notwithstanding a most profuse perspiration. On the following day she had quite recovered from the treatment and has since continued to improve.

April 26, after an all-night session, we were unable to locate a single microfilaria. The test was again repeated on May 10, with similar results. On the 24th, several microfilariæ were found on the 1 o'clock slides, and the medication was to have been repeated on the 29th. The weight of the patient had fallen from 400 pounds to 244 pounds, and her measurements on May 25 were as follows:—

	Right.	Left.
Thigh	32	31
Midthigh	25½	27
Knee	22	18
Calf	21	18
Ankle	14	13½
Instep	12	12¾

Blood examination on the same day showed:—

Hemoglobin	80 per cent.
Red cells	6,500,000
Leucocytes	5,800

The child's condition is now perfectly normal, as shown by the photograph,—weight 15½ pounds on May 25, 1912.

DISCUSSION.

Dr. Frederic H. Gerrish, of Portland, Me., said that the subject of filariasis had been more or less of a study with him for a number of years. The explanation of the manner in which dioxydiamidoarsenobenzol produced the results noted in this case would be extremely interesting. If it killed the *Filaria Bancrofti,* it effected a cure where there had never been a cure before. If it had not killed, but simply "scotched the snake," further trouble might be expected. This worm was possessed of great longevity, and it was possible that it might go on breeding as long as the individual harboring it lived. It would also be very interesting to know how Dr. Barnes's patient contracted her disease, and he would like to know whether there were any other cases of filariasis in the neighborhood. There were 11 varieties of mosquito capable of transmitting the filaria, but there was no variety of mosquito which was able to travel a great distance from the place of its birth. It would, furthermore, be interesting to know whether from the result in this case it could be assumed that arsenobenzol was a useful remedy in the treatment of obesity.

Dr. Barnes said that in this case the skin was very much relaxed. He had gone into the matter of travel thoroughly, in order to try to trace the origin of the disease. It was possible, he thought, that a mosquito might be carried for a long distance in fruit, etc. He had been entirely unable to locate the place of origin, and, as far as he

knew, there was no other case of filariasis in Washington or its vicinity. There must be, no doubt, some limit to the life-cycle of this worm. Whether he had succeeded in destroying the parent worms or not, a large number of the microfilariæ had certainly been got rid of. It seemed to him that the dead worm (which was of comparatively small size) might be absorbed, and that thus it would not interfere with the circulation. So far as recommending dioxydiamidoarsenobenzol as a remedy for this disease was concerned, he was simply reporting a case in which it had apparently produced a marked result, and he could only say that he would continue his careful study of this patient and at some future time give the outcome. In accordance with Dr. Gerrish's suggestion, he would also try the remedy in question in the treatment of obesity.

In reply to an inquiry from Dr. Gerrish, *Dr. Barnes* stated that there was no sign of syphilis about the baby.

Dr. Blackader said that, as we knew that arsenic was excreted in the mother's milk, it would be interesting to have this woman's milk examined from time to time.

Dr. Barnes said he would be glad to have the milk carefully watched.

DIOXYDIAMINOARSENOBENZOL IN THE TREATMENT OF VARIOUS CLINICAL FORMS OF SYPHILIS, WITH A REPORT OF TWENTY NEW CASES.

By JAMES M. ANDERS, M.D., LL.D.,

Professor of Medicine and Clinical Medicine in the Medico-Chirurgical College,

PHILADELPHIA, PA.

Notwithstanding the extensive trial accorded to this remedy since its introduction into the armamentarium of the therapeutician, its precise value is still imperfectly known. That the best results are obtained from the intravenous method of administration, followed by the intramuscular with a view to pocketing the remedy, as it were, so as to prolong its action, is probably a correct dictum. It is also generally conceded that following its administration treatment by mercury is necessary to bring about the most lasting effects. It may, however, be doubted whether the question of dosage has been determined with a sufficient degree of accuracy, and the same statement holds true of the numerous contraindications.

According to Ehrlich,[1] "the observation of the Wassermann reaction represents the most valuable method we have of seeing clearly whether the syphilis is genuinely cured." It must be admitted, however, that it is too early to state definitely what is the precise and the ultimate effect of the administration of arsenobenzol on the complement fixation test. It is also to be recollected that spirochetes may be demonstrated in the lesions in the presence of a negative Wassermann reaction, after the administration of arsenobenzol.

Again, a clinical relapse may be associated with a negative reaction for a considerable period of time, at least. The reaction, however, disappears in the majority of cases from two to five weeks after treatment by arsenobenzol, and this often occurs in cases in which the employment of mercury for a period of from one to several years had failed to cause its disappearance.

Billings[2] states that arsenobenzol "is undoubtedly of great value in early syphilis, and in syphilitics with gummatous infiltration and ulceration," and my experience accords with this opinion. He expresses grave doubt, however, if it will give us any better results than the rational use of mercury and the iodides. On the other hand, Meltzer[3] holds that arsenobenzol has some advantages over mercury. For example, it produces antibodies in the blood, while there is no evidence of the formation of these by mercury; its effect is much more rapid than that of mercury, and, finally, it acts favorably toward

1 Ehrlich, P.: "Chemotherapy," 1st ed., New York, p. 116, 1911.

2 Journal of the American Medical Association, November 18. 1911.

3 *Ibid.*, June 10, 1911.

the host, causing an increase of the weight of the patient, while mercury is inimical to the host, causing cachexia.

As already stated, the most satisfactory results are obtained from the rational use of arsenobenzol followed by mercury, or what might be termed the combined arsenozenzol and mercurial method of treatment, since each of these two agents exercises beneficial effects not shown by the other. In my earlier cases, after the introduction of arsenobenzol as a remedy in syphilis, I relied upon it exclusively, while later on its use was followed by that of mercury, with more gratifying results than when the former alone was employed.

Because of the fact that there exists considerable difference of opinion as to the efficacy of arsenobenzol as compared with that of mercury, and also regarding other points referred to above, observers should continue to record their individual experiences with the use of this new remedy, the rather voluminous recent literature on the subject notwithstanding. For a similar reason, the writer has been led to report the following cases:—

Case I.—Mrs. F. E., aged 31 years, referred by Dr. P. H. Lane; admitted to the Medico-Chirurgical Hospital, November 9, 1910. Patient came complaining of mucous patches, ulcerative tonsillitis, and typical secondary lesions. Mercury had been administered for a short period without any improvement, perhaps due, in part at least, to the patient's intemperate habits,—cigarette smoking and whisky drinking. An ocular examination yielded normal findings, and the urine was found to be normal as well. November 9th, at 2 P.M., 0.5 Gm. of arsenobenzol was injected between the scapulæ. November 10th, the temperature rose to 99⅘° F. in the course of three hours, and remained at that level with slight fluctuation until the following morning, when it rapidly returned to the normal. Blood examinations were not made in this case. One-half hour after injection, the patient complained of sharp, shooting pains in the axilla and left breast, which continued for two hours, after which they subsided. On November 11th, she complained of feeling weak, though having no pain. The eruption had faded in great part, while the mucous patches had entirely disappeared. On November 21st the skin lesions, mucous patches and ulcers in the throat had all disappeared, and there was no induration at the site of injection. Two weeks after the date of injection, however, pus was liberated from the site of needle puncture and continued to flow until July 5, 1911, when signs of healing commenced to appear. In August, 1911, examination of the blood for the Wassermann reaction was negative. The patient has had no return of any of the specific lesions to date, December 15, 1911.

Case II.—Mr. C. C., aged 25, referred by Dr. John A. McKenna. Occupation, clerk; negative family and previous histories. Contracted chancre March 14, 1910, and began treatment with mercury immediately. Shortly thereafter, he developed secondary lesions on the face, trunk, and extremities. The eye-ground, examined by Dr. L. Webster Fox, showed nothing abnormal, and the urine analysis gave a negative result. An examination of the blood resulted as follows: Erythrocytes, 4,460,000; hemoglobin, 80 per cent.; leucocytes, 7600. The Wassermann reaction was weakly positive (+). At the time of admission to the hospital, there were visible several dry, yellowish-white and scale-covered syphilides, varying from one to four lines in diameter, over both legs, below the knees anteriorly and posteriorly. Two small syphilides of similar character were seen on the skin between the thumb and forefinger of the left hand. The toe-nails were all devitalized, many having been shed, while the finger-nails were similarly affected, although not quite so extensively. On November 27, 1910, 0.5 Gm. of arsenobenzol was administered in neutral suspension intramuscularly under the right scapula. One hour later, pain began just below the site of injection, radiating to the right axillary and infra-axillary regions; it lasted about twelve hours, then gradually subsided. Some

degree of soreness at the site of injection remained, but no mass was present, as in the previous cases. An examination of the blood two days after the injection revealed a slight leucocytosis,—11,000. No febrile reaction followed the injection. At the end of one week the patient left the hospital, showing at the time but slight improvement as regards the eruption, although this was less scaly. He returned six weeks later, at which time the eruption consisted of mere light-yellowish, scar-like spots without any scales, while the nails were being reproduced and showed a healthy, natural appearance. A Wassermann reaction at this period gave a negative result. On July 22d, Dr. McKenna reported that the lesions had entirely faded and the patient was in good health. A Wassermann reaction taken January 18, 1912, proved strongly positive (+++), though there were no visible lesions at that time.

Case III.—Miss B. J., aged 31 years, referred by Dr. H. Brooker Mills. Occupation, housework. Following primary infection, six years ago, she developed a rash on the thorax, which disappeared in the course of six weeks as the result of treatment. Two years later a different form of eruption appeared, together with alopecia and amblyopia. Two years ago an ulcer on the left leg appeared, and, later still, neuromuscular pains. The patient was intelligent and well nourished. In the lumbar region was a large, copper-colored, pigmented scar, and numerous similar spots, though smaller, varying in size from a pea to a cent, were present on the left arm. There were two in the bend of the right elbow, one on the right wrist, and several over the left thigh. The left calf showed an area, twice the size of a dollar, on which there were four little ulcers, one nearly healed. Another small ulcer with irregular contour and about one-third of an inch in diameter was seen on the inner aspect of the right leg. The left ankle showed an area of similar color, covered by scales and presenting the appearance of healed ulcers. An examination of the eye-ground proved negative; likewise a urine analysis. A blood examination showed slight symptomatic anemia, the leucocyte count being 13,200. On the other hand, a Wassermann test was found to be markedly positive (+++). On December 1, 1910, at 5 P.M., 0.5 Gm. of arsenobenzol was injected under the right scapula. The temperature rose to 100° F. by midnight, then continued at that level during the next twenty-four hours, after which it rose to 101° F. for a short period, and then declined, reaching the normal December 6th. The local symptoms, which were unusually severe, abated with the decline of the fever. A blood examination revealed the following: Erythrocytes, 4,240,000; hemoglobin, 85 per cent.; leucocytes, 14,200. On December 5th, it was observed that the pigmented spots were gradually fading, and two days later one of the ulcers had healed, while the others were much smaller. On December 12th, the patient left the hospital with ulcers practically healed and other lesions greatly improved. On January 17, 1911, the patient returned; the Wassermann test gave a positive reaction (+++). The lesions were the same as previously described, though much less marked. On January 19, 1911, 0.5 Gm. of arsenobenzol was injected after the Alt method,—10 c.c. into each buttock. Slight pains were subsequently complained of. A very slight rise in the temperature ensued, but no induration or tenderness locally. A blood examination showed: Erythrocytes, 3,700,000; hemoglobin, 80 per cent.; leucocytes, 7200. The differential count was as follows: Polymorphonuclear neutrophiles, 58 per cent.; small lymphocytes, 28 per cent.; large lymphocytes, 12 per cent., and eosinophiles, 2 per cent. On January 21st, the leucocyte count was 12,600, but on January 23d, 24th, 25th, and 26th no abnormal increase in the leucocytes was detected. Four days after the injection, our records showed that the lesions were disappearing, and they continued to fade during the next few days, or until the patient left the hospital. The patient returned on April 4, 1911, with the lesions about the same as when she had left the hospital. The Wassermann reaction was still positive (+++), while on July 5th it was negative. No improvement having taken place in the lesions, 0.4 Gm. of arsenobenzol was injected intravenously into the right arm and mercurial treatment by mouth was resumed. On November 9th, patient reported that the lesions had faded since the last injection, especially those on the arms. The

Wassermann reaction was negative on December 28, 1911. Two days later, 0.45 Gm. of arsenobenzol was injected intravenously; no febrile reaction occurred. Following the injection, the lesions on the arms became almost imperceptible, and those on the lower extremities also showed improvement.

Case IV.—C. W., aged 30, referred by Dr. Robert H. Bolling. Occupation, merchant. Admitted December 1, 1910. About five years ago he contracted a primary sore, followed by secondary lesions. Ever since the date of primary infection, treatment was continued. About two months ago, he developed mucous patches in the mouth and noticed enlargement of the inguinal and postcervical glands. Since then he has had recurrences of mucous patches in mouth. The Wassermann reaction was positive (+). An eye-ground examination by Dr. Carl Williams gave negative results, and the urine analysis showed the kidneys to be healthy. On December 3d, at 12.30 P.M., 0.5 Gm. of arsenobenzol (6 c.c., neutral suspension; Wechselmann method) was injected in the right buttock. There was pain for a couple of hours, after which it was practically nil, although slight soreness remained for some days. The temperature after the administration of arsenobenzol gradually rose to 100° F. by 9 P.M., and then as gradually declined, reaching the normal level by 9 A.M. on the following day. The patient left the hospital without permission on the second day following the injection. In the course of six weeks from the date of the injection, he returned to his physician, Dr. Bolling, with a mucous patch in the mouth. A second injection was advised by his physician, but he refused to have it done. He was now given the usual treatment by mercurial preparations. Six months after the injection, Dr. Bolling reported that the lesions had disappeared under the above treatment.

Case V.—Mr. C. D., aged 32, referred by Dr. Ernest M. Dorsett. Occupation, baker. Entered the Medico-Chirurgical Hospital, December 2, 1910. The primary lesion developed September 1, 1910. Within forty-two days, this lesion healed, although it broke out again three weeks ago. Twenty-one days after the initial lesion, an eruption appeared, principally over the abdomen and beneath the scapula posteriorly; it lasted five weeks, and disappeared without leaving any trace of its former presence. Mucous patches occurred during the progress of the rash and have continued to recur until now. The physical signs were negative at the time of admission, except that several mucous patches in the mouth were visible. There was also marked gingivitis due to salivation. The urine analysis and eye examination both proved negative. A blood examination made just prior to the injection (December 3d) showed the following: Erythrocytes, 5,250,000; hemoglobin, 95 per cent.; leucocytes, 7400. The Wassermann reaction was positive (+ + +). On December 3d, at 1.30 P.M., the patient was injected in the right gluteal region with 0.45 Gm. of arsenobenzol after the Wechselmann method. Immediately after the injection, he experienced sharp pain in the buttock, radiating down the leg, which persisted till 11 P.M., when it gradually disappeared. On the following morning some slight degree of soreness remained, but no pain. On December 5th, the pain reappeared at the site of injection. The mucous patches were now gradually disappearing, and the pains persisted at intervals until December 9th. The mucous patches healed progressively, and on December 9th the process was complete. The temperature rose gradually after the injection and at 9 P.M. was 99.4° F.; it then declined and touched the normal level at 9 A.M. without subsequent rise. On December 7th, a blood examination revealed leucocytosis (13,000). On December 9th, a blood examination gave the following result: Erythrocytes, 4,620,000; hemoglobin, 90 per cent.; leucocytes, 11,000. On March 21, 1911, four months and a fortnight after the first injection, the patient returned with mucous patches in the mouth, several on the lower lip one-half inch in diameter and two smaller ones on the upper lip. The Wassermann test proved negative. At 4.30 P.M. an injection of 0.5 Gm. of arsenobenzol was given, in the left gluteal region only. March 22d, the temperature, which had been slightly elevated, was normal. A blood examination revealed the following: Erythrocytes, 4,600,000; hemoglobin, 85 per cent.; leucocytes, 12,600. On March 23d:

Erythrocytes, 4,800,000; hemoglobin, 80 per cent.; leucocytes, 10,600; differential count showed polymorphonuclear neutrophiles, 58 per cent.; small lymphocytes, 30 per cent.; large lymphocytes, 10 per cent., and eosinophiles, 2 per cent. On March 26th, the mucous patches were almost gone, although still covered with a whitish "scum." The patient stated that he could not feel them. The left buttock was still slightly tender (not painful), and there was slight induration. On May 20th, he called and stated that he felt well; no lesions were discoverable. (Dr. Dorsett has not seen him since the second injection.)

Case VI.—Mr. W. V., aged 26, referred by Dr. Franckson. Occupation, shuttle-maker. Admitted December 7, 1910. Contracted specific infection two years ago, the initial lesion appearing three weeks after intercourse. This lesion healed in the course of twelve days, and seven weeks later an eruption appeared upon the chest and arms, symmetrically. During the same period he suffered from malaise, languor, and glandular enlargement, particularly in the groins. As the result of treatment, the eruption cleared away, but for the last four weeks he has had a mucous patch on the right cheek, opposite the last molar tooth. There was also a history of previous smaller mucous patches at other points in the mouth. The patient has had mercurial gingivitis, which, however, was not present at the time of admission to the hospital. Prior to the injection of arsenobenzol, the physical signs consisted of alopecia and a large mucous patch on the right cheek, near the angle of the jaw. An eye-ground examination proved negative, and the same was true of a urine analysis. The Wassermann reaction was strongly positive. On December 9, 1910, at 1.30 P.M., an injection was given of 0.45 Gm. of arsenobenzol (Alt method), 10 c.c. being thrown into each gluteal region. Pain developed immediately and persisted until 5 P.M.; it was described as a constant ache, extending from the buttocks downward to and below the knees. On December 11th, the mucous patch was improving; there was no pain, but some soreness at the site of injection. December 12th, the mucous patch was found to be healing from the periphery; there was some induration at the site of puncture. Eight days after the administration of arsenobenzol, the mucous patch had entirely healed. The patient did not return for a second Wassermann test.

Case VII.—Mr. C. H. B., aged 33. Occupation, merchant. Admitted December 10, 1910. Confirmed cigarette smoker. In the spring of 1902, was infected, and about one week later an eruption appeared; primary incubation, fifteen days; sore throat associated with rash. Has had punched-out sores on the inner side of the lip from time to time. Has been under continuous treatment since 1902, with occasional outbreaks of symptoms. The palms of the hands showed scaly syphilides at the time of admission, and also reddish, indurated areas, less scaly, on the soles of the feet. The urine and eye-ground, examined by Dr. L. W. Fox, proved normal. A blood examination gave the following result: Erythrocytes, 5,020,000; hemoglobin, 96 per cent.; leucocytes, 8200. The differential count was as follows: Polymorphonuclear neutrophiles, 68 per cent.; small lymphocytes, 26 per cent.; large lymphocytes, 5 per cent.; eosinophiles, 0.8 per cent.; mast cells, 0.2 per cent. Dr. Batroff had reported two Wassermann reactions negative on October 24, 1910. On December 10, 1910, the Wassermann reaction was found, however, to be weakly positive (+—). Arsenobenzol, 0.5 Gm., was injected at 1 P.M. in alkaline solution (Alt method); 10 c.c. in the left and 8 c.c. in the right gluteal region. Pain at the sites of injection lasted about four hours, extending down to the knees and also up the back, although it was not constant. On December 11, 1910, the patient had passed a good night, experiencing no pain. The temperature showed slight elevation, to 99.1° F., at 9 P.M., but it fell to the normal during the night. On December 13th, a blood examination revealed the following: Erythrocytes, 5,012,000; hemoglobin, 93 per cent.; leucocytes, 10,000. The differential count: Polymorphonuclear neutrophiles, 71 per cent.; small lymphocytes, 13 per cent.; large lymphocytes, 15 per cent.; eosinophiles, 1 per cent.; mast cells, none. December 14th, four days after the administration of arsenobenzol, the patient felt well; soreness was practically nil, and the scales

on the hands had disappeared. On December 27th, patient was examined and scaly syphilides on the hands found nearly gone, though a small area persisted in each palm. The spots on the feet had dried completely. January 6, 1911, the hands were perfectly clear; general condition good. January 21, 1911, the Wassermann reaction was weakly positive (+). On June 30, 1911, the patient returned with scaly spots on the palmar surfaces of the fingers. On October 30, 1911, the eruption showed no improvement under mercurial treatment. The Wassermann reaction at that time was negative. On December 26, 1911, a large scaly syphilide (circinate) was present on the palmar surface of the right hand and the Wassermann reaction was still negative. An intravenous injection of arsenobenzol, 0.45 Gm., was given on December 31, 1911. Following the injection, the temperature rose to 100⅕° F. (it had previously been 99⅕° F.), but quickly returned to normal. The leucocyte count was 10,200. Seventy-two hours later, the eruption showed some improvement, and at the end of three months the patient reported its complete disappearance.

Case VIII.—Mr. M. H. J., aged 24, referred by Dr. Edward B. Gleason. Occupation, telephone repairer. Admitted to the Medico-Chirurgical Hospital, December 8, 1910. Had contracted initial lesion six weeks prior to the date of admission. Five weeks thereafter, an eruption made its appearance; it was bilateral, symmetrical, and principally roseolar in character. It had in great part faded when he came under observation. Mucous patches appeared in the mouth concomitantly with the eruption, and also postcervical glandular enlargement, with pain in the neck. At the time of admission, physical examination showed the presence of a scar on the outer surface of the left leg, one inch by one-half inch in diameter; also a somewhat smaller scar on right side of forehead. Over the back and chest anteriorly there was a fine papular eruption with symmetrical distribution; also on the outer surface of the left arm. Nearly all accessible lymphatic glands were slightly enlarged. The gums receded and were inflamed, with considerable pyorrhœa alveolaris. The teeth were in poor condition. Both tonsils were covered with a yellowish ulceration, and another, about the size of a dime, was present on the posterior wall of the pharynx. An ulcer was seen on the uvula. The mucous patches showed a strong tendency to spread. December 14, 1910, at 9.30 A.M., a report on the urine from the laboratory was negative. The Wassermann, however, was positive (+ + +). The blood showed oligochromemia of moderate degree, and there was hypotension. At 6 P.M. 0.4 Gm. of arsenobenzol was injected by the Alt method (10 c.c. in the left and 11 c.c. in the right buttock). There was marked fibrillary twitching at the site of injection in this case, and the patient complained of cramp-like pain. On December 15th, the patient had severe local pain for two hours after the injection, since which time he has been able to repose on his back with comfort. The ulcers in the mouth were already improving; the temperature rose somewhat, to 100⅕° F., in the course of a few hours after the injection had been made, but it declined to the normal as early at 11 A.M. of the next day, then rose again to 99⅖° F. for a twelve-hour period, after which it returned to the normal and there remained. It is interesting to note that just before the injection the leucocyte count was normal; also on the following day, but showed an increase of 11,600 on December 16th. Later it subsided, and on December 22d was again normal. Immediately after the injection, the hemoglobin was 85 per cent. and it kept at that level during the patient's stay in the hospital. On December 17th, the patches on the tonsils and pharynx were healing rapidly, and the skin eruption was fading. December 21st, the throat was quite clear, but the skin not entirely so, although improving. Slight tenderness was present at the point of injection. Three days later, the skin had practically cleared. Nothing could be learned of patient's condition after he left the hospital.

Case IX.—Mr. L. W., aged 51 years. Occupation, plumber. Admitted to the male medical ward of the Medico-Chirurgical Hospital, January 4, 1911. Specific infection in 1904; ten days later, an eruption appeared, followed by condylomata and slight alopecia. More recently, he had suffered from headaches. A physical examination

at the time of admission showed numerous patches over the scalp arranged in the form of wheals, especially in the occipital region. These were covered with grayish scales, which left a bleeding surface when they were removed. A number of mucous patches in the mouth and a pigmented area in left lumbar region, probably the site of a former gumma, were also noted. An examination of the eye-grounds by Dr. L. Webster Fox a few days previous to admission showed them to be entirely normal. The urine analysis was also negative. The blood showed moderate oligocythemia, oligochromemia, and leucopenia. The Wassermann test gave a strongly positive reaction (+ + + +). January 4, 1911, at 4 P.M., 0.5 Gm. of arsenobenzol was injected by the Alt method into both gluteal regions. Fibrillary tremor followed, more marked on the left side. Practically no suffering was associated with the administration of the remedy. There was a slight rise of temperature, which attained its maximum at 8 P.M. (99.8° F.); on the following morning, it had returned to the normal, and it remained there throughout the remainder of the patient's stay in the hospital. There was some induration at the site of puncture, with slight tenderness to pressure. No leucocytosis followed the injection of arsenobenzol in this case. January 7, 1911, the scaly patches were beginning to diminish in size. January 19th, two weeks after the injection, the eruption had practically disappeared. February 3d, the patient returned; the scalp was now clean and the general condition excellent. July 18th, the patient was still free of eruption and mucous patches. August 16th, the skin was clear, though the Wassermann reaction was positive (+ +). On February 1, 1912, the reaction was weakly positive (+), and ten days later 0.5 Gm. of arsenobenzol was injected intravenously. Since then no clinical symptoms of the disease have manifested themselves.

CASE X.—Mrs. P. C., aged 25 years, referred by Dr. C. N. Russell. Occupation, housewife. Admitted January 5, 1911. The patient had been married seventeen months before, and one month previously had had a miscarriage. The primary lesion was observed two months prior to her entrance in the hospital. An eruption appeared on the trunk and forearms immediately after the miscarriage, and subsequently she developed pharyngitis and glossitis. Snuffles were also present, while the postcervical and inguinal lymphatics were enlarged. The physical examination revealed a few papular elevations on the trunk and arms, as well as a few pigmented marks over the back and left forearm. The face showed a few pits. The Wassermann reaction immediately after admission to the hospital was strongly positive (+ + + +). An eye-ground examination was negative, and the blood revealed the following: Erythrocytes, 3,900,000; hemoglobin, 85 per cent.; leucocytes, 6400. A differential count gave: Polymorphonuclear neutrophiles, 68 per cent.; small lymphocytes, 23 per cent.; large lymphocytes, 8 per cent.; transitionals, 1 per cent., and eosinophiles, none. January 5, 1911, at 1 P.M., 0.45 Gm. of arsenobenzol was injected after the Alt method,—10 c.c. into each gluteal region. Considerable pain developed at once, which persisted with a tendency to increase until relieved by morphine, gr. ¼ hypodermically, in the evening. The temperature rose to 100⅖° F. at 11 P.M., and continued at 100° F. until 9 A.M. the next morning, after which it quickly fell to the normal. January 7th, patient said that she did not sleep well, and complained of generalized soreness and sore throat. On inspection, the throat was seen to be congested, but neither deposits nor ulcers were visible. At the same time the temperature ascended from the normal to 99⅘° F., and fluctuated between that level and the normal during the next two days, when the other local and general symptoms, including soreness about the elbow and hip joints, also subsided. January 6th, a blood examination revealed a result similar to that noted above; on January 7th, the leucocytes rose to 9600; on January 9th, to 12,600, and on January 11th and 12th they were found to be 6800 and 7600, respectively. January 9th, the spots were fading, while on January 11th the eruption presented a decidedly faded appearance and the pigmented spots were disappearing. On February 15th, the patient returned to hospital for a Wassermann reaction, which proved negative. The skin lesions had entirely faded and patient felt well. In August, 1911, no lesions

were present, and the Wassermann reaction was negative, but, as the patient was pregnant, an intravenous injection of arsenobenzol (0.6 Gm.) was given by Dr. Edward B. Finck. On December 16, 1911, Dr. Finck gave another intravenous injection of 0.6 Gm. for its effect on the fetus in utero. On January 17, 1912, the Wassermann reaction was negative, and there was no clinical evidences of syphilis.

Case XI.—Mr. C. T., aged 34 years, referred by Dr. Chas. G. Steinmetz, Jr. Occupation, butcher. Admitted to the Medico-Chirurgical Hospital, January 9, 1911. Contracted specific disease October 15, 1910, the initial lesion appearing twelve days after exposure. About December 1st, he observed that his hair was beginning to fall out, and a slight rash appeared on the legs and forearms, which has since disappeared. Recently, his throat has become sore and his tongue fissured. The physical examination revealed an adult male of large stature and well nourished; the skin was clear except that a few papules were seen over the legs and hips and on the anterior aspect of the chest. The inguinal glands were slightly palpable. The tongue showed a median fissure about one inch in length. The urine analysis proved negative, and the same was true of an examination of the eye-ground, made by Dr. Fox. The blood examination prior to the use of arsenobenzol gave the following result: Erythrocytes, 3,750,000; hemoglobin, 80 per cent.; leucocytes, 8200. The differential count showed: Polymorphonuclear neutrophiles, 73 per cent.; small lymphocytes, 18 per cent.; large lymphocytes, 8 per cent., and eosinophiles, 1 per cent. The Wassermann test proved positive (++). January 9, 1911, at 1 P.M., 0.45 Gm. of arsenobenzol was injected according to the Alt method,—10 c.c. into each buttock. Considerable pain followed during the afternoon and night, so that the patient did not sleep. January 10th, the patient complained of some soreness, and there was marked induration at the site of injection. Moderate leucocytosis (11,200) was now present. A slight rise of temperature during the afternoon and night (99⅘° F.) had occurred, but the temperature was practically normal on the 10th. January 12th, the sore throat was improved; the pain at the site of injection gradually diminished, with slight induration. January 14th, the throat and tongue were practically healed, and the buttocks were slightly sore. A blood examination showed a leucocyte count of 8800, while on January 15th it was 12,200. One month later, an examination of the blood-serum for the Wassermann reaction gave a weakly positive result (+). Dr. Steinmetz reported that, as no further improvement had occurred after the patient left the hospital, a second injection of arsenobenzol (0.4 Gm.) had been given intravenously. Three weeks later the Wassermann reaction was negative, though no change had occurred in the tongue.

Case XII.—Mrs. J. M., aged 29 years, referred by Dr. Carl Weiland, Jr. Occupation, housekeeping; American. Admitted to the Medico-Chirurgical Hospital, January 9, 1911. The patient had one child, 2½ years of age and in good health. The patient was infected October 12, 1910, but had no recollection of any primary lesion. Two or three weeks after exposure, there developed copper-colored spots on the arm and, in fact, quite generally; this was accompanied with fever and pharyngitis in the course of a day or two. General examination revealed a young, white female of small stature and poorly nourished. The postcervical, submaxillary, and inguinal glands were palpable. The skin was pale, moist, and showed a macular eruption on the forearms and the legs below the knees, with a tendency to desquamate. The edges of the tongue were inflamed; the center coated. The throat showed an ulcerated patch on the left tonsil, but was otherwise negative. The Wassermann reaction was found to be positive (+++). Examinations of the eye-ground and of the urine gave negative results. A blood examination revealed the following: Erythrocytes, 3,900,000; hemoglobin, 90 per cent.; leucocytes, 9400. January 10th, at 11.30 A.M., 0.45 Gm. of arsenobenzol was injected after the Alt method (10 c.c. in each gluteal region). Pain followed: it was dull in character, and continued up to 6 P.M., when it was relieved by a hot-water bottle. January 11th, the temperature touched 101⅘° F., but fever had already been present prior to the administration of the remedy. The evening temperature remained elevated

for three days after the injection. A blood examination revealed the following: Erythrocytes, 3,900,000; hemoglobin, 85 per cent.; leucocytes, 11,000. The systolic blood-pressure was 120. January 12th, there was slight pain at the site of injection; the rash had already faded and the throat was improved. There was some generalized soreness, a bad cough, and dull, aching pains in knees. January 14th, the temperature was normal; the throat showed continued improvement; the eruption was dry and faded; the patient still had aching pain in the knees and hip; the cough was better. A blood examination made January 12th showed: Leucocytes, 8400; January 16th, 7800, and January 17th, 8200. January 18th, the rash on the legs and arms had almost disappeared. The throat was in good condition; pain in knees was very slight. The patient showed evidences of mild arsenic poisoning (dermatitis and slight diarrhea), which, however, soon cleared up. The specific lesions disappeared rapidly and have not recurred. Since leaving the hospital, the patient has had two intravenous injections at another institution. She is free from symptoms. The Wassermann test has not been repeated.

Case XIII.—Mr. G. U., aged 21 years, referred by Dr. J. Hamilton Small. Occupation, draughtsman. Admitted to the Medico-Chirurgical Hospital, January 9, 1911. Primary specific lesion contracted November 15, 1910, and still present. A papular eruption on the arms and legs appeared one week before admission, together with sore throat and swollen glands on the right side of the neck. A positive Wassermann reaction was obtained (+++); the eye-ground proved negative (Dr. Fox), and the same was true of the urine analysis. A blood examination gave the following result: Erythrocytes, 4,200,000; hemoglobin, 90 per cent.; leucocytes, 7800. A differential count gave: Polymorphonuclear neutrophiles, 62 per cent.; small lymphocytes, 26 per cent.; large lymphocytes, 10 per cent., and eosinophiles, 2 per cent. January 10, 1911, at 12 o'clock noon, 0.45 Gm. of arsenobenzol was injected after the Alt method,—10 c.c. into each gluteal region. The patient experienced dull, aching pain at the site of injection during the afternoon and evening, with fibrillary tremors. The temperature rose to 100.5° F.; pulse, 98. January 11th, the patient complained of generalized soreness and dull, aching pain at the site of injection; slight leucocytosis (10,800). January 12th, the papules were fading; soreness at the site of puncture was only slight. The large lymphatics in the neck were gradually decreasing in size. January 14th, the rash was fading more and more, and the patient felt well; slight local soreness was still present. On March 4th, the patient returned with secondary papular syphilides over the body. A Wassermann reaction gave positive results (+++). The patient, however, failed to present himself for further injections and could not be located.

Case XIV.—Mr. P. L., aged 43 years, referred by Dr. Samuel Lowenburg. Occupation, provision business. Specific infection occurred about September 15, 1910. Two weeks later, a chancre appeared on the genitals, and on November 3, 1910, a mucous patch was seen on the upper lip. On February 2, 1911, the Wassermann reaction being weakly positive (+), 0.6 Gm. of arsenobenzol (alkaline solution) was injected intragluteally at the patient's home. There was some febrile reaction, ranging from 99 to 101° F., which subsided after a few days. The mucous patches healed rapidly, and the patient was free from lesions until June 27th, when several mucous patches reappeared in the mouth. The Wassermann reaction at this time was positive (+++), while the eye-ground was negative. On July 8, 1911, the patient was admitted to the Medico-Chirurgical Hospital, and 0.4 Gm. of arsenobenzol was injected intravenously. This was followed by no discomfort, febrile reaction, or leucocytosis, and the lesions quickly healed. Following this injection, mercurial treatment was instituted, but three months later several mucous patches returned. A third injection of arsenobenzol (0.5 Gm. intravenously) was given on October 25, 1911, after which rapid disappearance of the lesions took place. During, and for several hours after, the patient complained of pain in the gums and teeth, together with numbness in the tongue and lips. On April 3, 1912, Dr. Lowenburg reported that there had been complete absence of symptoms since the last injection.

Case XV.—Mr. H. K., called July 2, 1906, presenting slight secondary manifestations. Specific infection had occurred two months previously. Treatment by means of mercury was administered continuously for a year or more, and then intermittently until the present. All secondary symptoms disappeared in the course of two months, and then followed a long period of freedom from symptoms. More recently, from time to time, a tertiary skin eruption (rupia) appeared, amenable to treatment by mercury, as a rule. On January 17, 1911, a Wassermann test was weakly positive (+). On February 7, 1911, the eye-ground and urine analysis having both given negative results, arsenobenzol (0.4 Gm. in alkaline solution) was injected in the gluteal regions. No febrile reaction occurred and no leucocytosis was found either on February 8th or 10th. The skin cleared in the course of two weeks, and the eruption has not, thus far, recurred. On May 4th, the Wassermann reaction was doubtfully negative (±), and on August 9th a distinctly negative reaction was obtained. On April 22, 1912, patient reported that no skin lesions had recurred, and that he felt perfectly well.

Case XVI.—Mr. J. B., aged 20 years. Occupation, bartender. Admitted February 20, 1911. The patient was addicted to the excessive use of alcoholic liquors. Specific infection occurred November 11, 1910. Eruption and sore throat followed on January 3, 1911, since which time mucous patches have appeared. The mouth and throat have been worse for the past three weeks. General examination revealed a well-nourished, rational male: the skin showed a few papules and pustules on the face. The hair was falling; a large mucous patch was noted on the lip and another on the mucosa of the cheek; the throat was inflamed, but not ulcerated, and otherwise negative. An eye examination and a urine analysis showed nothing abnormal. Neither were there any other contraindications. February 20, 1911, at 1 P.M., 0.6 Gm. of arsenobenzol was injected, the alkaline method being used and 10 c.c. administered in each buttock. February 21, 1911, patient had passed a good night, and complained of no pain in the buttocks. A slight rise of temperature (100⅕° F.) occurred during the night, but at 10 A.M. this day the temperature had returned to the normal. February 22d, the blood showed slight leucocytosis (10,000); the secondary lesions showed no change. February 23d, the mucous patches showed a tendency to heal; the rash had faded; the leucocytes were diminished. February 26th, the small mucous patch had healed, while that on the lip was healing rapidly; the skin lesions were scarcely perceptible; the general condition was good. The patient left the hospital. Since that time there has been no recurrence of symptoms; the patient has been taking mercury.

Case XVII.—Capt. K. W., aged 41 years, referred by Drs. George Friebis and C. F. Chandler. Occupation, soldier, U. S. A. The initial lesion occurred twenty years ago, and was followed by well-marked secondary manifestations, at which time he was given a very brief course of constitutional treatment. Early in 1911, the patient consulted Dr. Friebis because of failing vision, and an examination of the eye-ground revealed a low-grade neuroretinitis of luetic origin. On March 20, 1911, the Wassermann reaction was strongly positive (+ + +), and, on March 28th, 0.45 Gm. of arsenobenzol (alkaline solution) was injected intramuscularly at the patient's home. Following the injection, the patient was given mercurial treatment by mouth. Two months later, there was some improvement in the vision, and the Wassermann reaction was feebly positive (+). Five months later, or on October 29th, the patient returned, and an examination of the eyes showed them to be absolutely normal; no other symptoms of the disease were present. The Wassermann reaction at this time was negative.

Case XVIII.—Mr. K. F. H., aged 23 years. Medical student. Infected April 10, 1911; three weeks later, two chancres appeared on prepuce, and the patient was admitted to the hospital on May 23, 1911. At that time the chancres were still present, with some enlargement of the inguinal glands. The Wassermann reaction was strongly positive (+ + + +); Dr. O. F. Mershon found the eye-ground normal. An injection of 0.4 Gm. of arsenobenzol (alkaline solution) was given in the gluteal regions. This

was followed by severe cramp-like pain, which was permanently relieved by an injection of morphine. There was no febrile reaction, but on the following day there was a leucocytosis of 14,800, with 52 per cent. of lymphocytes. The patient left the hospital, going to his home in Oil City on May 25th, with slight improvement in the lesions; healing, however, was completed ten days after the injection. On July 23d, secondary lesions appeared in the throat, but these healed after seven days of mercurial treatment. October 14, 1911, the patient reported that he had been salivated; secondary lesions consisting of a few papules on the back and a small mucous patch on the right buccal mucous membrane appeared later; the mercurial treatment was being continued in small doses.

Case XIX.—Mr. G. W. B., aged 48, referred by Dr. I. C. Gable. Occupation, merchant. Specific infection occurred in 1897, for which he was treated one year ago, with disappearance of the secondary manifestations. In 1904 his memory became impaired and some mental confusion, together with defective vision, developed. In 1905 the patient had a partial right hemiplegia, which gradually cleared up. An examination of the eyes by Dr. de Schweinitz at this time revealed a marked hemianopsia, which temporarily improved under heroic doses of mercury and iodide. The patient first came under my observation on December 6, 1911, at which time he complained of defective vision, poor memory, and depression of spirits. The Wassermann reaction was strongly positive (+++). The systolic blood-pressure was 132 mm. Hg. The physical examination gave negative results, except for exaggerated tendon-reflexes. An examination of the eyes by Dr. L. Webster Fox revealed hemianopsia, but no retinal changes. On January 9, 1912, 0.3 Gm. of arsenobenzol was injected intravenously. The patient returned on March 6th, much improved as regards vision and mental condition. He had gained 5 pounds in weight. A second dose of 0.4 Gm. of salvarsan was now given. Neither injection was followed by either febrile reaction or leucocytosis. On April 5, 1912, Dr. Gable reported that the second injection had not been followed by any perceptible improvement.

Case XX.—Mr. F. V. C., aged 37. Occupation, salesman. Specific infection was contracted in April, 1904, and later the secondary manifestations appeared. These yielded in great measure to treatment, but the late secondaries showed a tendency to recur, up to about one year ago. At that time, the Wassermann reaction was found to be weakly positive (+). The patient felt well and was not inclined to subject himself to treatment by arsenobenzol. January 9, 1912, a second Wassermann test was made, which gave a similar result, and one month later the patient received 0.5 Gm. of arsenobenzol intravenously. This was followed by slight leucocytosis (12,200) and a mild febrile reaction lasting three days. The fever may have been caused by the presence of a considerable local reaction, which has since disappeared, with induration of the arm for some distance above the wound. The effect upon the general condition of the patient was most favorable, although no opportunity for making a Wassermann test has since then presented itself.

Remarks.—There are a few facts shown by the above series of cases that are worthy of brief mention. In the first place, the sentiment of most writers on the subject and my own limited experience indicate the far-reaching favorable effect of the remedy in syphilis. As regards the more rapid action of arsenobenzol than of mercury, this is also confirmed by the majority of the foregoing reports, especially Cases I, II, III, V, VI, VII, IX, XI, XIV, XV, XVI, XVII, and XIX.

When I adopted the combined use of arsenobenzol and mercury in the manner described above, the tendency to relapses seemingly became less evident, although the number of injections given has been too few to base trustworthy

deductions thereon; this likewise accords with the experience of other observers. Whether, however, it will be found true of all cases of syphilis, and whether certain unknown factors enter into the question, can only be decided after more extended clinical observations.

I have found the Wassermann reaction absent at times in latent cases with slight secondary and tertiary lesions, *e.g.*, in Cases III, V, and VII. In such circumstances, we may assume safely that too few spirochetæ are present to produce a reaction, but that if we administer arsenobenzol, sufficient organisms may be destroyed to liberate the stimulus needed to produce enough antibodies to give a + or + — reaction. This occurred in Case VII after injection of 0.45 Gm. of arsenobenzol. Such positive reactions, however, are of short duration, as a rule. On the other hand, a positive reaction may be present in the absence of recognizable clinical symptoms, as in Cases II, VII, IX, and XX; this is to be regarded as a sign of active internal syphilis.

A principal reason for failure to cure syphilis by the use of arsenobenzol is, in many cases at least, the insufficient number of doses administered by clinicians, the patients often receiving but a single injection. It is important to repeat the dose if we would completely sterilize the body of the syphilitic patient. Certain it is that the best way to prevent relapses is by repeated injections of arsenobenzol. Fortunately, this remedy does not produce strains of spirilla resistant to itself, as was formerly supposed.

The injections should be made, when practicable, at intervals of about eight weeks, for three or four doses in succession, unless a relapse occurs earlier, in which event an injection should be administered without delay. An exception to this rule should be made in those instances in which a negative Wassermann is found repeatedly following the first or second injection of arsenobenzol, and all recognizable symptoms of the disease have disappeared.

Wechselmann's[4] method of distilling and sterilizing the water for the saline used in the solution of the arsenobenzol immediately before the treatment has recently been adopted by me (I employed it in the last seven injections), with the same results as were previously obtained from the use of solutions similarly prepared once weekly.

4 Wechselmann: Deut. med. Woch., xxxvii, 778, 1911.

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